COLLECTED PAPERS

of

THE MAYO CLINIC

ROCHESTER, MINNESOTA

EDITED BY

MRS. M. H. MELLISH

VOLUME VIII

1916

FOREWORD

In order to maintain a reasonable size for the present volume of Collected Papers, a few of the articles read or published by the staff of the Mayo Clinic in 1916 have been omitted entirely, and several have been presented in the form of abstracts. In addition, a number of others, that did not completely fulfill the requirement of previous publication, have been held over and will be included later in more comprehensive studies on the same subjects.

MRS. MAUD H. MELLISH

Editor

ROCHESTER, MINNESOTA
June, 1917

iii
365431

LIST OF CONTRIBUTORS

ARCHIBALD, ALEXANDER, M.B., CH.B. (Edinb.), Head of Section Seven, Division of Medicine;* Volunteer Fellow in Internal Medicine.†

BALFOUR, DONALD C., M.B., M.D. (Tor.), F.A.C.S., Head of Section Four, Division of Surgery;* Associate Professor of Surgery.†

BECKMAN,‡ EMIL H., PH.B., M.D., F.A.C.S., Head of Section Four, Division of Surgery;* Associate Professor of Surgery.†

BERKMAN, DAVID M., B.S., M.D., First Assistant in Section Three, Division of Medicine;* Volunteer Fellow in Internal Medicine.†

BLACKFORD, JOHN M., M.D., First Assistant in Section Two, Division of Medicine;* Volunteer Fellow in Internal Medicine.†

BRAASCH, WILLIAM F., B.S., M.D., Head of Section on Urology, Division of Medicine;* Professor of Urology.†

BRODERS, ALBERT COMPTON, M.D., First Assistant in Section Two, Division of Pathology;* Volunteer Fellow in Pathology.†

BUMPUS, HERMON C., PH.B., M.D., Fellow in Surgery (Urology).†

CARMAN, RUSSELL D., M.D., Head of Section on Roentgenology, Division of Medicine;* Professor of Roentgenology.†

CHASE,¶E. FRANK, M.D., First Assistant in Section on Rhinology and Laryngology;* Volunteer Fellow in Rhinology and Laryngology.†

CRENSHAW, JOHN L., M.D., First Assistant in Section on Urology, Division of Medicine;* Volunteer Fellow in Surgery (Urology).†

CRISPIN, EGERTON L., PH.B., M.D., Fellow in Internal Medicine.†

DURANTE, LUIGI, M.D. (Genoa), Fellow in Surgery.†

EUSTERMAN, GEORGE B., M.D., First Assistant in Section One, Division of Medicine;* Assistant Professor of Medicine.†

FISHER, CARL, B.S., M.D., F.A.C.S., Head of Section on Ophthalmology and Otology, Division of Medicine;* Associate Professor of Ophthalmology and Otology.†

FOSS, HAROLD L., M.D., First Assistant in Section Two, Division of Surgery.*

FRELIGH, WILFRED P., A.B., M.D., Fellow in Surgery.†

* In the Mayo Clinic.
† On the Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota.
‡ Deceased.

GIFFIN, HERBERT Z., B.S., M.D., Head of Section Six, Division of Medicine;* Associate Professor of Medicine.†

HENDERSON, MELVIN S., M.B., M.D. (Tor.), F.A.C.S., Head of Section on Orthopedics, Division of Surgery;* Associate Professor of Orthopedic Surgery.†

JUDD, EDWARD STARR, M.D., F.A.C.S., Head of Section Three; Division of Surgery;* Associate Professor of Surgery.†

KENDALL, EDWARD C., B.S., A.M., PH.D., Head of Section on Biochemistry, Division of Pathology;* Assistant Professor of Biochemistry.†

LITTLE, GEORGE G., M.E., Instrument Maker.*

LUDEN, GEORGINE, ARTZ, M.D. (Munich), Volunteer Fellow in Pathology.†

MACCARTY, WILLIAM C., B.S., M.S., M.D., Head of Section Two, Division of Pathology;* Associate Professor of Pathology.†

MANN, FRANK C., A.B., A.M., M.D., Head of Section One, Division of Experimental Surgery and Pathology;* Assistant Professor of Experimental Surgery and Pathology.†

MAYO, CHARLES H., A.M., M.D., LL.D., F.A.C.S., Head of Section One, Division of Surgery;* Professor of Surgery.†

MAYO, WILLIAM J., A.M., M.D., D.Sc., LL.D., F.R.C.S., F.A.C.S., Director of Division of Surgery;* Head of Section Two, Division of Surgery.*

MOORE, ALEXANDER B., M.D., First Assistant in Section on Roentgenology, Division of Medicine;* Assistant Professor of Roentgenology.†

NEW, GORDON B., D.D.S., M.B., M.D. (Tor.), Head of Section on Rhinology, Laryngology and Stomatology, Division of Medicine;* Assistant Professor of Rhinology, Laryngology, and Stomatology.†

PLUMMER, HENRY S., M.D., Director of Division of Medicine;* Head of Section Two, Division of Medicine;* Professor of Medicine.†

PLUMMER, WILLIAM A., M.D., Head of Section Three, Division of Medicine;* Volunteer Fellow in Internal Medicine.†

ROBINSON, SAMUEL, A.B., M.D., Head of Section on Thoracic Surgery, Division of Surgery;* Assistant Professor of Surgery.†

ROSENOW, EDWARD C., M.D., Director of Division of Experimental Bacteriology;* Professor of Experimental Bacteriology.†

SANFORD, ARTHUR H., A.B., A.M., M.D., Head of Section on Clinical Laboratories, Division of Medicine;* Associate Professor of Clinical Bacteriology and Parasitology.†

* In the Mayo Clinic.
† On the Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota.

STACY, LEDA J., M.D., Second Assistant in Section One, Division of
    Medicine;* Volunteer Fellow in Internal Medicine.†

STOKES, JOHN H., A.B., M.D., Head of Section on Dermatology and
    Syphilology, Division of Medicine;* Assistant Professor of Medi-
    cine.†

THOMAS, GILBERT J., M.D., Assistant in Section on Urology, Division of
    Medicine.*

TOWNE, EDWARD B., A.B., M.D., Volunteer Assistant in Division of
    Experimental Bacteriology;* † Assistant in Surgery, Peter Bent
    Brigham Hospital, Boston.

WHEELER, GEORGE W., M.D., Resident Pathologist, New York Hospital,
    New York City.

WILLIUS, FREDERICK A., B.S., M.D., Second Assistant in Section Two,
    Division of Medicine;* Volunteer Fellow in Internal Medicine.†

WILSON, LOUIS B., M.D., Director of Division of Pathology;* Head of
    Section One, Division of Pathology;* Professor of Pathology.†

YOUNG, THOMAS O., B.S., Medical Student, University of Minnesota;
    Temporary Assistant in Section One, Division of Pathology.*

MRS. M. H. MELLISH, *Editor*

* In the Mayo Clinic.
† On the Mayo Foundation for Medical Education and Research, Graduate School,
University of Minnesota.

CONTENTS

ALIMENTARY CANAL

ALIMENTARY CANAL

BLASTOMYCOSIS OF THE TONGUE *

GORDON B. NEW

Blastomycosis is usually considered a skin lesion or a systemic disease. In a review of the literature I have been able to find only one case of blastomycosis of the tongue. Copelli[1] in 1913 reported a case of a woman who presented a tumor of the tongue consisting of an aggregation of six rounded nodules on the back part, with some enlargement of the sub-maxillary glands. She had also blastomycetic lesions on both feet. Examination revealed the blastomyces in the affected tissues. The treatment used and the end-results are not stated. I wish here to report a case of blastomycosis of the tongue examined in the Mayo Clinic:

J. S. M., man, aged fifty-two, chief of fire department, came to the Clinic February 7, 1916, for tumor of the tongue, which had been first noticed eleven months previously. The family history was not important. Thirty-two years previously he had had a chancre, which, from the history, was questionably specific. He had no secondary lesions. He smoked and chewed moderately, but had not used alcohol for thirty-one years. Sixteen months before examination at the Clinic he had had tonsillitis and was treated by a physician. Eleven months before he had received an electric shock from touching an electric fixture with his right hand. On the following morning he noticed that his tongue was larger than usual. The next day he consulted a physician, who found a tumor at the base of the tongue and removed specimens for diagnosis. These specimens were reported as being "mostly lymphatic gland containing much granulation tissue; no evidence of malignancy or tuberculosis." Electric treatments for the tongue were given at this time. Nine months before coming to the Clinic he was given five treatments with neosalvarsan and eleven injections of sodium cacodylate, with no resulting change in the tumor. At this time he had much difficulty in swallowing and talking. A month later he consulted a physician who diagnosed the condition as lymphadenoma and cauterized the tumor several times with an electric needle. This was done once a week over a period of two months. There had been shortness of breath for eight months, and also great difficulty in swallowing solids, though fluids were

---

* Reprinted from Jour. Amer. Med. Assoc., 1917, lxviii, 186–188.

[1] Copelli, M.: "A Case of Blastomycosis," Gior. ital. d. mal. ven., 1912, liii, 467. Abst. in Jour. Cutan. Dis., 1913, xxxi, 51–52.

swallowed readily. The tumor seemed to be increasing in size, but no swellings in the neck were noted. The patient had lost 60 pounds since the onset of the trouble, and found it almost impossible to sleep at night as the tongue fell back and obstructed the pharynx, causing dyspnea. The normal weight had been 220 pounds; weight at the time of examina-
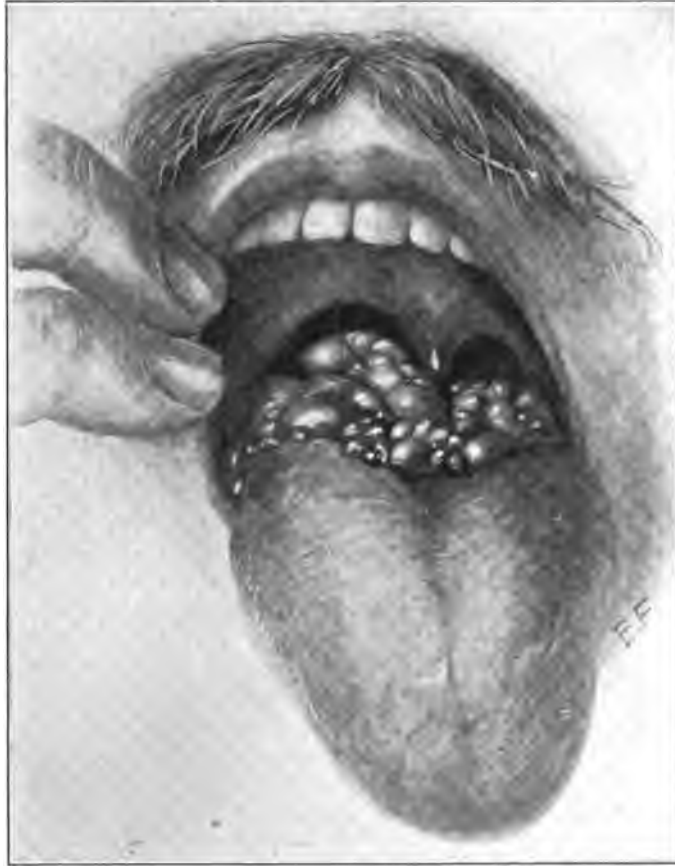
Fig. 1.—Blastomycetic tumor of the tongue.

tion, 150 pounds. Speech was difficult; the voice was thick and mostly nasal in character.

Examination of the mouth showed a nodular tumor at the base of the tongue filling the entire pharynx, so that the postpharyngeal wall was not visible. It was impossible to press down the tongue in order to examine the posterior part of the growth. The tumor was quite firm, but did not have the hardness of malignancy. It appeared in rounded folds between which were grayish-white areas. There were no lesions in other

parts of the mouth. The systolic blood-pressure was 110, diastolic blood-pressure 70, pulse 96, temperature 98.6° F., urine negative. The white blood count was 5400, red blood count 5,270,000. Roentgenoscopy of the chest was negative as was also the Wassermann test. No lesions were found in any other parts of the body. The tissue removed from the tumor showed microscopically lymphoid hyperplasia with great numbers of plasma cells. Blastomycetes were found on culture from the areas in
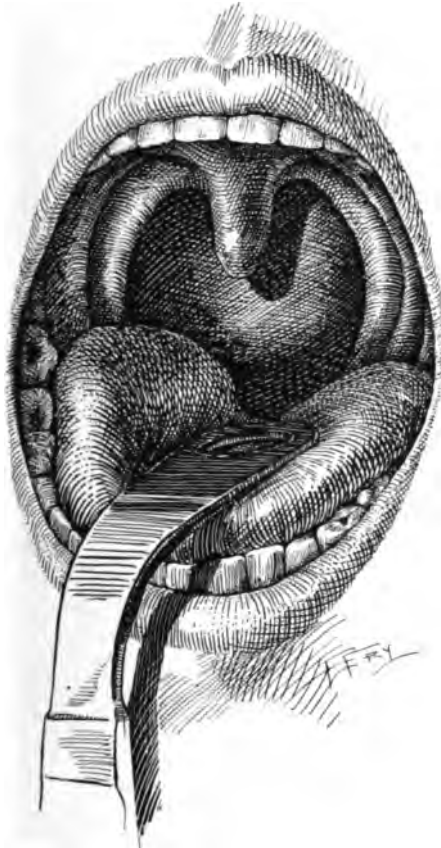
Fig. 2.—Same as Fig. 1 after condition had cleared up.

the folds of the tumor. A culture of blastomycetes injected into guinea-pigs yielded negative results.

A diagnosis of blastomycosis was made on the presence of blastomycetes with secondary lymphoid hyperplasia of the tissue of the tongue, and because all other findings were negative. Malignancy, tuberculosis, and syphilis can be readily ruled out by the data of the history and the appearance of the tumor. The patient was given potassium

iodid, ten drops three times a day, the dose being increased by two drops daily until 125 drops were taken three times daily. Iodin was used locally to swab the tumor once a day, and radium, twenty-six hours of a 22 mgm. tube, was given for a period of three weeks. Five weeks after this treatment the patient returned showing marked improvement in his general health. He was then able to eat and swallow without difficulty, had no dyspnea on exertion, and had gained 20 pounds in weight. The tongue showed remarkable improvement, and in a direct examination of the mouth very little of the tumor was visible. It was possible to see
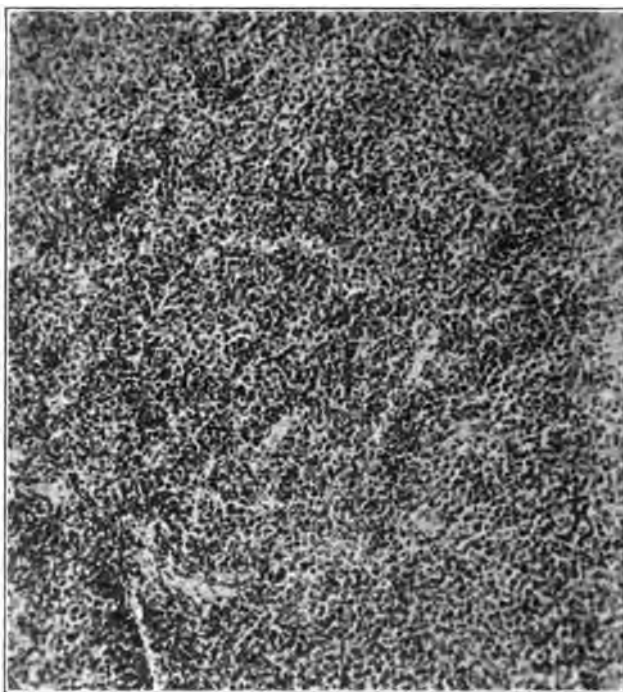
Fig. 3.—Low power: lymphoid hyperplasia.

the pharynx, and by the use of the laryngeal mirror it was found that the tumor extended down the base of the tongue to the epiglottis. Sixteen hours of a 50 mgm. tube of radium were then given for a period of two weeks, the iodin again applied locally, and the potassium iodid continued. Four weeks later the patient returned feeling perfectly well, eating and sleeping without any trouble. He had gained 15 pounds since his last visit. The tongue appeared normal on direct view, and it was possible to see the pharynx readily. By the use of a laryngeal mirror a nodular tumor 1½ inches in diameter was seen down at the base of the tongue. About it were several small nodular tumors. The larger one was re-
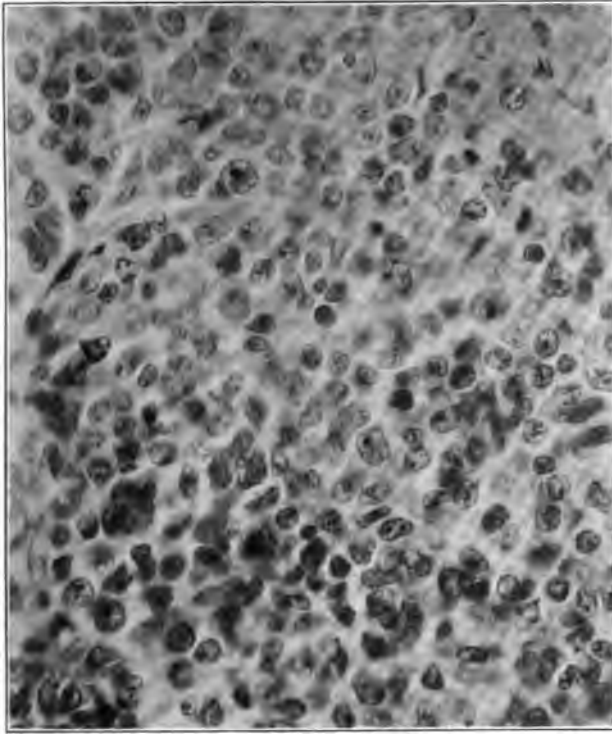
Fig. 4.—High power: great numbers of plasma cells and lymphocytes
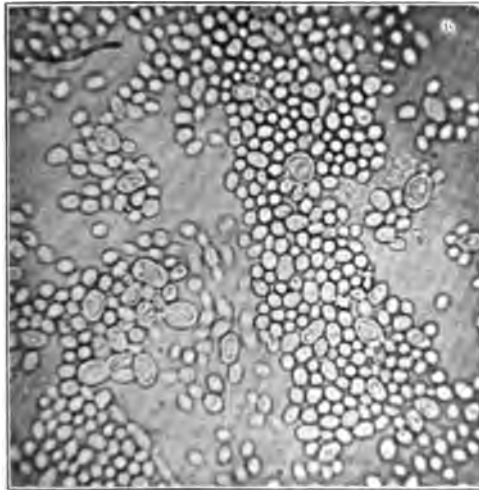
Fig. 5.—Pure culture: blastomycetes.

moved by a snare and forceps. On microscopic examination it showed pure lymphoid hyperplasia. The smaller nodules were treated with radium, sixteen hours of a 22 mgm. tube. Iodin was applied locally and the potassium iodid continued.

When examined again, August 10, 1916, the tongue was found normal. The patient had gained 16 pounds since his last visit, and was feeling well.

This case is of interest because of the rarity of blastomycetic lesion of the tongue and the remarkable results of the treatment. The nodular appearance of the tumor seemed to be the same as that reported by Copelli. It must be remembered, however, that blastomycetes may be found in the tonsils and lingual tonsil and that, therefore, the presence of blastomycetes alone does not necessarily mean that the disease is true blastomycosis. It would seem that the lymphoid hyperplasia was a secondary condition stimulated to growth by the presence of blastomycetes, possibly in the lingual tonsil.

RADIUM IN THE TREATMENT OF LYMPH-
ANGIOMA OF THE TONGUE *

GORDON B. NEW

The treatment of lymphangioma of the tongue until recently has been considered surgical, although the results obtained have not been very encouraging on account of the frequency of the recurrences of the condition and also the difficulties encountered in trying to make a useful organ out of a large, thickened, and more than useless tongue. Surgical measures have usually consisted in excising as much of the tumor mass as possible and then, by cutting out wedge-shaped pieces of tissue from about the margin of the tongue, attempting to construct a useful organ.

Abbe[1] reports three cases of lymphangioma of the tongue successfully treated by radium, and states that this type of tumor is one more condition which can be added to the list of those in which radium has a specific action. He states that the effect of radium on lymphangiomas is not destructive, but is an alterative action similar to its effect on papilloma or basal-cell epithelioma. He conjectures that the specific action of radium on lymphangioma is a charging up of the disordered cells of the tumor with negative electric particles, which latter, when shot into the cells in proper quantity, completely change their habit of growth and permanently restore them to a perfectly healthy condition. The tumor gradually shrinks and disappears and the tongue takes on its normal appearance and outline.

I report here two cases of lymphangioma of the tongue treated by radium at the Mayo Clinic:

CASE 144,540.—A. J., a girl, aged twelve years. The patient came to the Clinic October 29, 1915. She complained of the size of her tongue, which caused difficulty in eating and talking. Her father stated that she had been unable to put it back in her mouth for four years. Eight years ago the parents noticed that it was larger than normal and since that time it had been increasing in size. For the last two months the

[1] Abbe, R.: "Lymphangioma and Radium," Med. Rec., 1915, lxxxviii, 215–217.

Fig. 6.—(144,540.) Lymphangioma of the tongue.

Fig. 7.—(144,540.) Same as Fig. 6, two months after treatment.

Fig. 8.—(144,540.)   Same as Fig. 6, showing displacement of teeth by the large tumor

Fig. 9.—(151,037.)   Lymphangioma of the left half of the tongue.

increase in size had been more marked. During the last six weeks the patient had had 17 x-ray treatments with no improvement. Her lower central incisor teeth had been removed six months previously, as they were loosened by the tongue. Examination showed the condition of the tongue to be as illustrated in Fig. 6—typical lymphangioma. The patient was a pitiable sight. The tongue was dry and cracked and she was unable to draw it back into the mouth. It was impossible to understand what she said. She was treated with radium for two hours daily with a 22-mgm. tube, unscreened, for a period of twelve days. Two months after this treatment she returned to the Clinic showing the remarkable improvement evident in Fig. 7. Her tongue fell back into

Fig. 10.—(151,037.) Same as Fig. 9, two and one-half months after treatment.

her mouth readily but was still slightly thickened. She has received further radium treatment and her parents say she continues to improve. Fig. 8 shows the displacement of the teeth by the tongue.

CASE 151,037.—K. C., a boy, aged two and one-half years. When he was one year old his mother noticed a thickening near the center of the dorsum of the tongue, about the size of a pea. This condition spread over the entire left side of the tongue. The child had been examined several times by physicians but nothing had been done in the way of treatment. The left half of the tongue, as shown in Fig. 9, was much thickened, and the surface showed pearly papules and other areas that resembled an-

gioma. The condition was lymphangioma. The left side of the tongue was given two hours daily of a 28-mgm. tube of radium, unscreened, for a period of ten days. Soon after the treatment was begun a marked improvement was noticed. Fig. 10 shows the condition two and one-half months after treatment when the patient returned to the Clinic. The large tumor on the left side of the tongue had entirely disappeared, and the tongue felt and appeared normal.

These cases were treated by superficial application, but incising the tumor and placing the radium in the center of it gives good results in similar tumors. It would seem that radium is a specific for angioma and lymphangioma, and its great value is that it gives such remarkable results in these conditions which are not surgical. However, much is to be learned as to dosage and methods of applying the radium.

ADENOMA OF THE PALATE *

GORDON B. NEW

Neoplasms of the palate are commonly of a malignant nature, usually cancerous. They arise either in the palate itself or involve it from the nose, antrum, alveolar process, or pharynx. The benign growths include
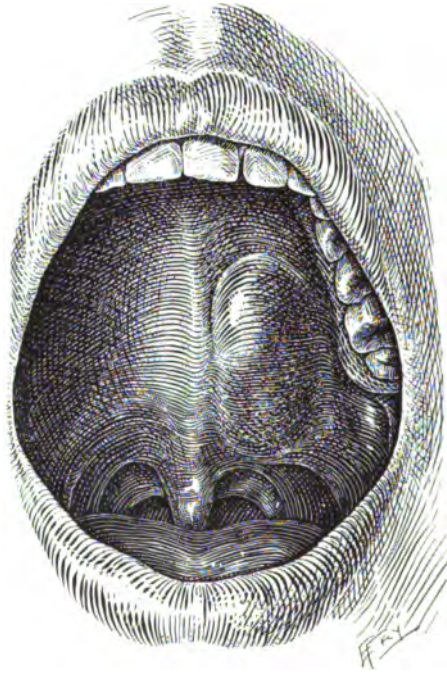
Fig. 11.—(157,265.) Cystadenoma of palate.

papillomas, angiomas, fibromas, osteomas, odontomas, lipomas, mixed tumors, adenomas, and other peculiar epithelial tumors. Adenomas of the palate are quite rare, although it seems hardly possible that they

are as unusual as appears from a study of the literature. Possibly the rarity of case reports is due to the fact that the tumor usually shells out readily and often no microscopic examination is made. Moreover, some observers have classified adenomas with mixed tumors of the palate, although true adenoma is distinctly different and quite easily distinguishable microscopically. The term "adenoma of the palate" has been used loosely to indicate a slowly growing benign tumor, and tumors are

Fig. 12.— (Same as Fig. 11.) Downgrowth of the epithelium from the normal epithelium.

at times reported as adenomas with no mention of the microscopic pathology of the growth.

Paget[1] reported 31 collected cases of clinical adenoma of the palate. He stated that the term adenoma in these cases is of clinical value only, implying nothing as to the microscopic appearance. In most of his cases there was no account of the microscopic pathology, and when present, such accounts had little in common.

Since Paget's report (1886) I have been able to collect from the literature only eight cases with a pathologic diagnosis and five cases reported

as adenoma without any microscopic pathologic diagnosis. This group seems far too small to represent the actual number of cases, but the factors already mentioned may account for the discrepancy.

Two cases of rare tumors of the palate reported herein have been seen in the Mayo Clinic: the first a case of true cystadenoma, and the second an equally rare epithelial tumor, but not a true cystadenoma.

CASE 1 (157,265).—C. K., school girl, aged sixteen years. Examined December 6, 1915. Tonsillectomy three years previously. Four days
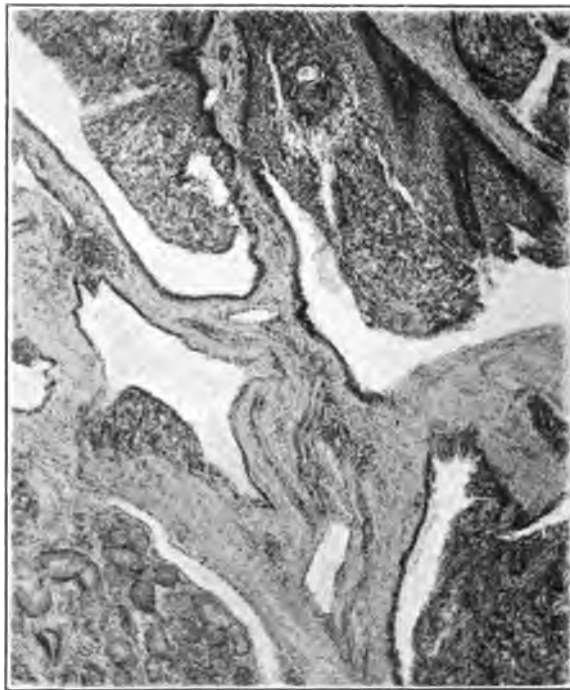
Fig. 13.—(Same as Fig. 11.)   Glandular structure of the tumor.

before examination a growth on the left side of the roof of the mouth was noticed; a physician was consulted, who punctured it, but did not take a specimen for diagnosis. He advised her to come for treatment immediately. It was not known how long the growth had been present; the girl believed that the left side of the roof of the mouth had always been larger than the right. There had been no other complaint; her general health was good, though she was very nervous. A tumor was found on the left side of the hard palate, 2 by 1½ inches, extending into the soft palate. It was fairly regular in outline, and the mucous membrane

covering it was normal except where it had been punctured. About this opening were signs of inflammation. The nose and sinuses were negative, and no glands were palpable in the neck. Wassermann negative. When a specimen was taken from the tumor for diagnosis, about an ounce of straw-colored sticky fluid was evacuated. Microscopic examination of the specimen showed a cystadenoma (Figs. 11, 12, 13, and 14).

On December 13, 1915, the tumor was removed under ether anesthesia. It was found limited to the soft tissues of the palate, and did not involve the bone, although an excavation was noticed where it had rested.
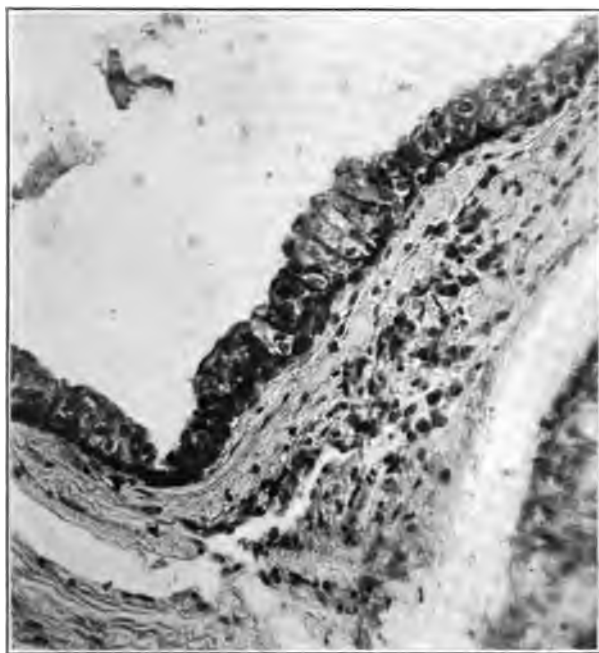
Fig. 14.—(Same as Fig. 11.) High magnification of the glandular cells.

While the growth was readily dissected out, there was no definite encapsulation. The wound healed nicely and there is no recurrence to date.

CASE 2 (156,093).—L. M. P., male, aged sixty-four years. Examined March 29, 1916. The man came to the Clinic because of a growth on the left side of the palate, noticed one year previously. The tumor did not seem to be increasing in size, and he had no inconvenience from it. Two weeks previously he consulted a physician, who lanced the tumor twice. Nothing was evacuated and no further treatment was given. Except for this growth the patient was well. When examined, a tumor 1½ by 1 inch in size was seen on the left side of the palate at the juncture of

'16—2

the hard and soft palates. The mucous membrane was normal over the tumor except where it had been incised by the home physician; the tumor was freely movable.

On March 3, 1916, the tumor was excised under local anesthesia. The growth was definitely encapsulated and easily shelled out. The wound healed readily. Microscopically the growth proved to be a peculiar epithelial tumor (Figs. 15, 16, 17, and 18).

Fig. 15.— (156,093.) Unusual epithelial tumor of the palate.

Adenomas of the palate may occur at any age. The youngest patient was a girl aged sixteen years, reported in this paper, and the oldest a man aged sixty-five years, reported by Escat[2] in 1897. In the group of proved cases collected, including the one I have reported, were eight females and one male. The duration of the tumor may be from one year to fourteen years, but often the growth has been found accidentally on examining the mouth. Often in cases of the smaller tumors no symptoms are complained of, but the growth may increase to such size as

to cause dyspnea and difficulty in swallowing. Dobson[3] reports fibro-adenoma so large that it could not be removed between the teeth. The tumor may be situated in the hard or the soft palate or may involve both. Most frequently it is seen on the left side. It is not characteristic in appearance. The mucous membrane generally appears normal and unbroken, although Hutchinson[4] reports two cases in which the surfaces were deeply ulcerated. In one case the ulceration resembled the crypts
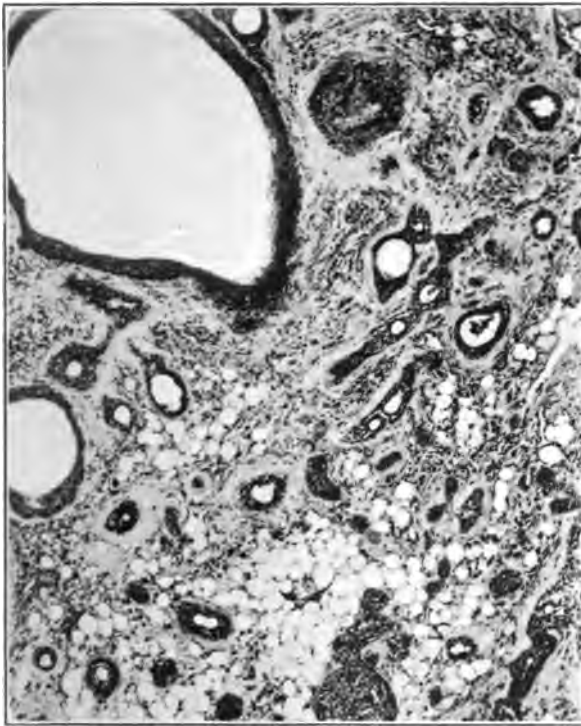
Fig. 16.—(Same as Fig. 15.) Areas showing the cell nests. In other areas the central part of the nests has dropped out, leaving the outer layer of cells.

of a tonsil and contained cheesy material. In these two cases and Case 157,265 reported here, the tumors had diffuse margins with no definite capsule. In this respect they were quite different from those of other cases reported. Usually the growth is freely movable and rests in a saucer-like cavity in the bone like a dermoid. The tumor may be cystic, as that of Case 157,265 and the case reported by Marsden and White.[5] The outline and surface of the tumor are generally regular. No glandular

enlargement was noted in any case reported. King,[6] however, reports a case in which the base of the tumor passed outward and backward behind the jaw and could be felt externally. In order to remove the tumor it was necessary to split the cheek. Dobson[3] reports a case in which the growth formed a swelling the size of a chestnut under the angle of the jaw. This swelling, however, we believe was an extension of the tumor rather than a gland.

Fig. 17.—(Same as Fig. 15.) Several areas where the central portion of the cell nests has dropped out.

HISTOGENESIS AND PATHOLOGY

Paget[7] states that pathologically these tumors are embryonic in character and resemble closely tumors of the parotid which are manifestly embryonic. Morton[8] says the fact that in these tumors the same cells differentiate into gland epithelium and embryonic connective-tissue cells of oval or spindle shape proves the embryonic origin of the tumor from an early stage in the fetal development, and indicates a close analogy

to the complex nature of the ordinary parotid tumor. MacCarty[9] believes, however, that they are not of embryonic origin, but develop from the germinative layer of the epithelium of the palate. The normal basal layer of this epithelium may develop squamous cells or differentiate into glandular cells. Although these two tumors originate apparently in the same cell group, they are two distinct types. In the one the basal cells have grown down and differentiated into glandular cells, forming the picture seen in the true cystadenoma. In the other the germinative
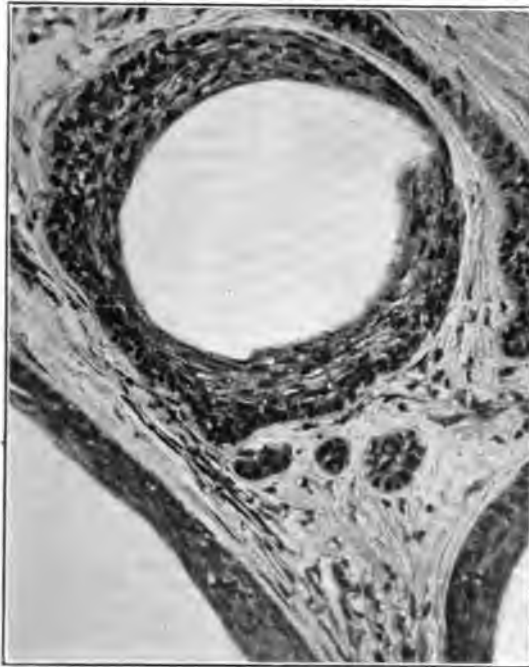
Fig. 18.—(Same as Fig. 15.) Character of epithelium in remains of cell nests (high magnification).

layer of the epithelium has formed squamous cells and cell-nests in its development. Areas are to be seen in which the differentiated cells are disappearing and others in which apparently they have dropped out entirely, the germinative layer alone remaining about the cavity. This theory as to the origin of these tumors seems by far the most plausible.

Most adenomas of the palate are encapsulated tumors, homogeneous on the surface and on section. Those reported by Marsden and White[5] and that in Case 157,265, however, were definitely cystic, containing

fluid. According to Morton,[7] the characteristic features of an adenoma
on microscopic examination are: (1) Cell-nests; (2) adenoid tissue; (3)
glandular structure, and (4) embryonic connective tissue. Hutchinson[4]
states that, in addition to these features, the tumors reported by him
showed immense numbers of acini like those of the salivary gland and
oral cavities filled with lymph-cells. The latter possess a regular fibrous
wall similar to that of the lymphoid follicles of the tongue, tonsils, etc.
It would seem that the term adenoma should be reserved for the type
of tumor showing the characteristics of Case 157,265.

DIAGNOSIS AND TREATMENT

In differentiating an adenoma from other types of tumors of the
palate it must be remembered that adenocarcinoma is not infrequently
found in this region and also that sarcoma may be present. This must
be taken into consideration particularly in the diagnosis of cases in which
the tumor is found accidentally and the history necessary to eliminate
malignancy is not obtainable. By far the safest plan is to excise a piece
of tissue for examination. An operation may then be performed with a
definite knowledge of the treatment indicated. When the tumors are
small, it is best to remove them under local anesthesia, as usually no
difficulty is found in excising them. When large, however, such as those
reported by Dobson[3] and King,[6] a more radical procedure may be
required.

REFERENCES

1. Paget, S.: "Tumors of the Palate," St. Bartholomew's Hosp. Rep., 1886, xxii, 315–352.
2. Escat, E.: "Adénome du Voile du Palais," Arch. prov. de chir., 1897, vi, 320–325.
3. Dobson, N. C.: "Tumor of the Soft Palate," St. Thomas Hosp. Rep., 1875, n. s., vi, 36–38. Quoted by Morton, loc. cit.
4. Hutchinson, J.: "Two Cases of Adenoma of the Palate with Exceptional Clinical Features," Tr. Path. Soc. London, 1886, xxxvii, 490–495.
5. Marsden, R. W., and White, C. P.: "A Peculiar Tumor of the Palate," Med. Chron., 1910, lii, 1–6.
6. King, K.: "Case of Tumor Originating in the Soft Palate and Protruding into the Isthmus of the Fauces, Removed by Operation," Lancet, 1871, i, 264. Quoted by Morton, loc. cit.
7. Paget, S.: "Tumors of the Palate," Tr. Path. Soc. London, 1887, xxxviii, 348–349.
8. Morton, C. A.: "'Adenoma' of the Soft Palate," Tr. Path. Soc. London, 1893, xliv, 59–62.
9. MacCarty, W. C.: "The Histogenesis of Cancer of the Stomach," Am. Jour. Med. Sci., 1915, cxlix, 469–476.

CYSTS OF THE LARYNX *

GORDON B. NEW

Cysts of the larynx are benign tumors and produce symptoms which depend on their size and location. Three of these cysts have recently been examined at the Mayo Clinic and are reported herewith.

CASE 1 (A130,087).—F. G. A., a married woman, aged twenty-six years, came to the Clinic October 7, 1916, because of difficulty in swallowing. She talked as if her throat were full. Eight months previously she first noticed trouble in swallowing. This had gradually increased. There had been no previous hoarseness, and she had been perfectly well. During the last month, when swallowing, fluids have been forced into her nose. There had been some dyspnea on exertion; her breathing was quite natural when she remained quiet. She complained that her throat was filled with mucus. For three weeks she could eat semi-solid food only, and for three days she had been unable to swallow anything. Her normal weight was 120 pounds. She had lost 15 pounds since the onset of the trouble. At the beginning of her symptoms a physician was consulted who said that her tonsils were enlarged, and treated her throat from time to time. Two weeks before the examination she had put her tongue
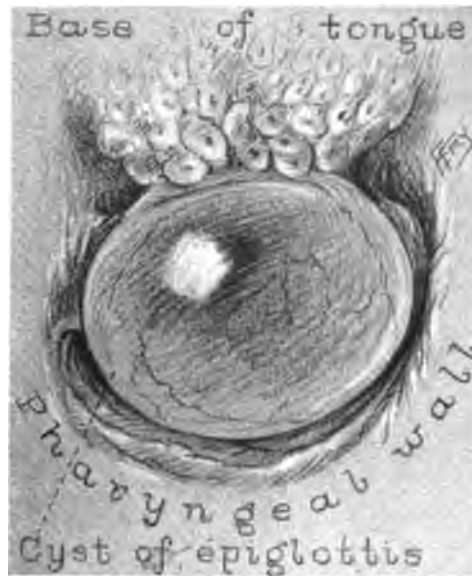
Fig. 19.—(Case A130,087.) Cyst of epiglottis showing cyst almost entirely filling pharynx.

Base of tongue

Phaɾyngeal wall

Collapsed cyst

Fig 20.—(Case A130,087.) Cyst collapsed following spontaneous rupture.

out of her mouth, and by depressing the base of the tongue discovered the tumor. The examination of the throat at the Clinic showed large tonsils, and upon pressing down the base of the tongue a rounded tumor was found filling the throat. With the laryngeal mirror it was seen that the tumor almost entirely filled the pharynx (Fig. 19). The tumor was cystic and apparently attached to the epiglottis or base of the tongue. The mucous membrane was grayish in appearance and there were several vessels on the wall of the cyst. The examination was made in the morning, and in the afternoon the patient returned saying that something had broken in her throat and she could swallow more readily. The tumor had ruptured spontaneously and was draining a thin, yellow seropus. The larynx had become visible, and the attachment of the cyst was seen to be the lingual surface of the right side of the epiglottis and a small area at the base of the tongue (Fig. 20). The cyst was removed by fixing its wall with a fixation forceps and the use of a snare. After its removal the base was thoroughly cauterized with an electric cautery. Fig. 21 shows the appearance three weeks after the operation.

Microscopic examination of the cyst-wall showed fibrous tissue in the lining and squamous epithelium on the outside (Fig. 22). The

Healing area

Pharyngeal wall

Fig. 21.—(Case A130,087.) Healing area which extends up onto the lingual surface of the epiglottis—three weeks following operation.
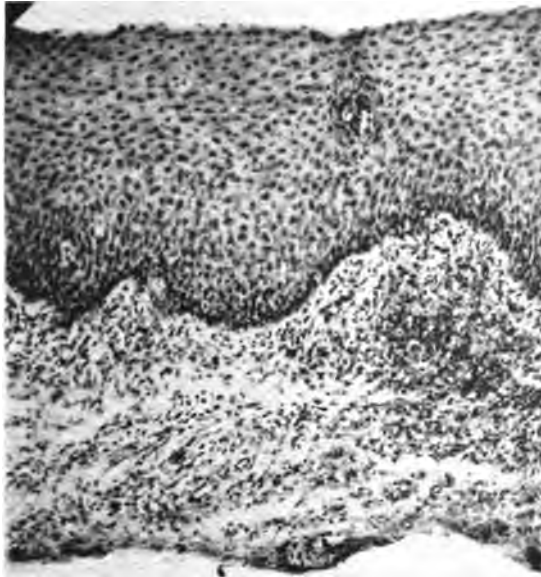
Fig. 22.—(Case A130,087.) Cyst-wall showing fibrous-tissue lining and squamous epithelium on outside.

pressure of the contents of the cyst apparently had destroyed any epithelial lining that may have been present. It seemed to be a retention cyst, and is of special interest because of its unusual size.

CASE 2 (A173,885).—W. A. McN., a married woman, aged thirty-six years, came to the Clinic September 28, 1916. She gave a history of hoarseness for four years, and was referred for examination on account of a goiter she had noticed six years previously and which she had been told was the cause of the hoarseness. She had had slight dyspnea on exertion for two years, but seemed well otherwise. Three months previously a physician had told her that she had a growth in her throat, but he was unsuccessful in removing it. The patient appeared well nourished, weighing 182 pounds.

Fig. 23.—(Case 173,885.) Cyst of the anterior third of the right ventricular band.

Height, 5 feet 4 inches. Blood-pressure, 104-76. She had a small adenoma of the thyroid, 1¼ by 1¼ inches in size, but otherwise the general examination showed nothing of note. In examining the larynx, a cystic tumor ¾ inch in diameter was found on the anterior third of the right ventricular band, which obstructed the approximation of the cords on phonation (Fig. 23). The tumor was removed, and the base cauterized with the electric cautery by the indirect method. The voice immediately became normal.

This case is of particular interest because of the fact that the laryngeal symptoms were due, not to the presence of a goiter, but to the intralaryngeal (retention) cyst. Microscopically the picture was the same as that in Case 1. The immediate restoration of the voice on removal of the cyst is an interesting feature, such as may be noted also after the removal of various other small benign neoplasms of the cords.

CASE 3 (A176,018).—J. F. W., a married woman aged forty-eight years. This patient came for examination October 27, 1916, because of nervousness and worry for fear she had cancer. In the routine examination the cyst of the lingual surface of the epiglottis was found, but there were no symptoms which could be attributed to the cyst even after the patient knew it was there. The cyst, 1 by ½ inch in size, was on the right side of the lingual surface of the epiglottis. It was yellowish in color, and there were blood-vessels over its surface (Fig. 24). It was removed with fixation forceps and a snare and the base cauterized. The cyst contained a dram of pus. Microscopically it showed the same characteristics as the tumors in Cases 1 and 2.

Fig. 24.—(Case A176,018.) Cyst of the lingual surface of the epiglottis.

The fact that this patient gave no symptoms of the presence of the cyst shows the futility of attempting definitely to state the length of time it had existed. At any time this cyst might have flared up, and if this

had occurred, the patient would have given only a short history of complaint, even though the cyst might have been present for years.

In 1863 Gibb[1] operated on a cyst of the vocal cord, the first case reported in the literature. In 1896 Michel[2] collected 44 cases of cysts of the epiglottis. The relative proportion of cysts to other neoplasms is shown in Beschorner's[3] report of a collection of 693 polypoid growths of the larynx, among which were 45 cysts (6 per cent.). Most laryngeal cysts are found on the anterior surface of the epiglottis. This statement is verified in Moure's[4] report of 117 cases of cysts of the larynx (epiglottis, 50; vocal cords, 45; ventricle of Morgagni, 8; arytenoid cartilage, 4; arytenoid epiglottic fold, 3; Santorini cartilage, 1; ventricular band, 2; location not indicated, 4).

Retention cysts may be located in any part of the larynx, but the most common situation is the anterior surface of the epiglottis and in the region of the ventricle where the mucous glands are most numerous. The embryonic types are found in the aryteno-epiglottic fold and on the lateral laryngeal wall. This would seem further to substantiate Schneider's theory that they are a part of the appendix of the ventricle. The other types of cysts due to the extravasation of lymph and blood are usually found about the vocal cords. Cysts may occur at any age. Their presence may cause death shortly after birth, as in the case reported by Porak and Theuveny,[5] in which the child lived only twenty-four hours. Necropsy revealed a cyst of the laryngo-epiglottic fold, the size of a cherry, obstructing the glottis. The chest examination in this case was negative. Greene[6] has found three cases of cyst of the epiglottis that caused death in the new-born. Cysts of the epiglottis are usually quite small—about the size of a pea; one the size of a hazelnut would be considered large. In 1907 Greene reported a cyst of the epiglottis a little more than an inch in diameter. He believes the one reported by Hamilton[7] in 1899, a cyst the size of a hen's egg, to be the largest on record. The cyst in Case 1 reported here almost filled the entire pharynx.

Etiology and Pathology.—A large majority of laryngeal cysts are retention cysts of the mucous glands of the larynx. This type may develop by the obstruction of a duct of a mucous gland and the accumulation of secretion. Two other types may be found, the first developing from the so-called embryonal origin, and the second due to the extravasation of lymph or blood into the subepithelial tissues. The embryonal type is called a congenital cyst, and may be present at birth or

develop later in life. There are several theories as to their origin. Schneider[8] believes that they are formed from a pinching off of the appendix of the ventricle of the larynx, and this would seem to be the most plausible explanation. Louys,[9] however, believes they are of branchiogenic origin, as the cyst he reported contained cartilage. He says that the mesodermic tissue developing this would come from the mesodermic tissue of the branchial arches. Von Kostanecki and von Mielecki,[10] in their work, have not found that at any time in embryonic life the pharyngeal pouch comes in relation to the trachea or larynx. This would seem to throw doubt on Louys' theory as to branchiogenic origin. Glas[11] has pointed out that the location of the embryonic laryngeal cysts is the meeting-point of several germinal layers, but this is not supported on an embryonic basis, inasmuch as all epithelial parts belong to the entoderm. Beck[12] brings up the question as to the etiology of these cysts from the thyroglossal duct tissue, but this hypothesis does not seem well founded. It has been said that laryngeal cysts are due to the echinococcus. Schüssler[13] published one such case, but the etiology is questionable.

Retention cysts, when of short duration, are lined with columnar epithelium. The cyst-walls of the three cases in this series did not have epithelial tissue, but contained fibrous tissue as their inner lining. Squamous epithelium was present on the outside of the cyst-wall. The disappearance of the lining epithelium in the cyst is due to the pressure of its contents. The same condition is seen in cysts in other locations in the body.

Embryonal cysts have an epithelial lining, and the cyst-wall contains numerous glands. Schneider states that the diagnosis of the embryonic type in his case was made on the presence of numerous glands and much elastic tissue in the cyst-wall, in which were small lymph-follicles.

Treatment.—In some cases laryngeal cysts have been punctured and have apparently disappeared. The best method, however, is to remove the cyst-wall and cauterize the base where the cyst was attached by the indirect, the direct, or the suspension method, whichever the individual case may indicate. The treatment of the embryonic type may present greater difficulties, and a thyrotomy may be necessary in order to eradicate the cyst.

REFERENCES

1. Gibb: In Heinze, Arch. f. Laryngol., 1880, i, 24. Cited by Louys, *loc. cit.*
2. Michel, Y.: "Contribution à l'étude des kystes de l'epiglotte," Thèse de Bordeaux, 1896. Cited by Louys, *loc. cit.*

3. Beschorner: "Ueber Epiglottiscysten," Berlin. klin. Wchnschr., 1877, xlii, 620. Cited by Louys, *loc. cit.*

4. Moure: Étude sur les kystes du larynx, Paris, 1881. Cited by Louys, *loc. cit.*

5. Porak and Theuveny: "Kyste du larynx," Compt. rend. Soc. d'obst., de gynec. et de pædiat. de Paris, 1902, iv, 150.

6. Greene, D. C., Jr.: "An Unusual Cyst of the Larynx," Laryngoscope, 1907, xvii, 800–804.

7. Hamilton: Montreal Med. Jour., August, 1899. Cited by Greene, *loc. cit.*

8. Schneider, P.: "Zur Genese der kongenitalen Larynxcysten," Ztschr. f. Ohrenh. und f. d. Krankh. d Luftwege, 1911–12, lxiv–v, 358–374.

9. Louys, E.: "Des kystes intralarynges et en particulier des kystes larynges branchiogenes," Thèse de Geneve, Paris, 1900.

10. von Kostanecki, K., and von Mielecki, A.: "Die angeborenen Kiemenfisteln des Menschen; ihre anatomische Bedeutung und ihr Verhältniss zu verwandlen branchiogenen Missbildungen," Arch. f. path. Anat., 1890, cxx, 385; cxxi, 55; 247. Cited by Louys, *loc. cit.*

11. Glas, E.: "Ueber Larynxcysten," Arch. f. Laryngol. u. Rhinol., 1906–7, xix, 285–305. Cited by Schneider, *loc. cit.*

12. Beck, J. C.: "Cyst of the Epiglottis," Laryngoscope, 1909, xix, 704. Cited by Schneider, *loc. cit.*

13. Schüssler: "Beobachtung einer Hydatidenbildung im Kehlkopf eines Kindes," Med. Cor.-Bl. der Württemb. Aerzt. Ver., Stuttgart, 1848, xviii, 75–77. Cited by Louys, *loc. cit.*

ELECTIVE LOCALIZATION OF THE STREPTOCOC-
CUS FROM A CASE OF PULPITIS, DENTAL NEU-
RITIS, AND MYOSITIS *

EDWARD C. ROSENOW

Localized infections in or about the roots of teeth have already been considered in causal relationship to systemic disease and to neuralgia of the face. Experimental proof of the nature of this relationship, however, is still undetermined. In this paper I wish to record the history of a case in point and the results of experiments which appear to throw light on the subject.

CASE 567.—Mrs. F. H. P., aged thirty-five years, had been subject to severe migraine for many years. For the past five or six years she has suffered from recurring attacks of neuralgia of the face, which began with severe pain and distinct swelling over the left upper jaw, spreading to the opposite side, with soreness in the teeth, especially in the upper jaw, and followed by intense pain in the left side of the head, neck, and shoulders. During the last two or three years the attacks have occurred oftener and had grown so severe as to necessitate the frequent use of hypodermics of morphin; the attacks have ended with spasm of the muscles, and tenderness and swelling of the neck on the left side. The tonsils were removed four years ago, but this did not relieve the condition. One year ago the second left upper molar, showing a blind abscess at the root, was extracted, the left maxillary sinus drained, and a piece of the left turbinate removed, but without relief. The patient became extremely nervous, at times hysteric, during the paroxysmal pain, and has had one or two spells of mental confusion suggesting petit mal. Previous to tonsillectomy she had had for years one or more attacks of tonsillitis followed by rheumatic pains during the winter months.

Examination revealed a poor vasomotor tone, moderately firm muscles, and fair nutrition. The general appearance was that of a nervous woman. On January 13 the hemoglobin was 85 per cent.; the leukocytes, 9800. A Wassermann test of the blood proved negative. On February 17 the hemoglobin was 80 per cent.; the erythrocytes, 4,210,000; the

leukocytes, 5400. There were no signs of organic disease of the central nervous system. The examination of the heart, lungs, abdomen, reflexes, urine, roentgen examination of the jaws, roots of teeth, and the blood-pressure, were all negative. There was tenderness over the left infra-orbital foramen and mental foramen, but no superficial tenderness of the overlying skin. Tender nodules, which appeared to be enlarged glands, were noted in the posterior triangle of the left side of the neck. There was a clean tonsillectomy scar, a normal condition of the nose except moderate hypertrophic rhinitis, and a normal condition of the gums and teeth, except a tender dead first upper left molar which had been crowned, but from which the crown had been removed on account of the irritation of the gums. The maxillary sinuses were clear. Owing to the fact that each attack began with swelling of the left upper jaw opposite the dead tooth and in the region of the left infra-orbital fora-men, the tooth was extracted January 18. There was found a semi-lunar eroded area, 2 mm. in diameter, near the apex of the largest and inner fang. The surface of this was sterilized with a searing blade, and the root-canal drilled into from the apex with a dental burr. The pulp-cavity was filled with foul-smelling pus. The erosion was situ-ated so that it was impossible to be shown by the roentgen ray. The pulp-cavity of the other two fangs was filled and obliterated and there were no erosions at the apices. There was a large cement filling directly opposite the dead pulp. Smears from the pus from the root showed a few Gram-positive diplococci, diphtheroid bacilli, and a few Gram-nega-tive bacilli. The primary cultures in ascites-dextrose agar and broth gave a pure culture of a slightly hemolyzing streptococcus. The an-aërobic cultures on blood-agar slants and in tall columns of ascites fluid containing sterile tissue, covered with paraffin oil, had a foul odor and many short chains of streptococci and numerous bacilli resembling Bacillus fusiformis.

Immediately after the extraction of the tooth the patient developed an unusually severe attack, but she gradually recovered after several exacerbations. On February 17, after she had been free from pain for ten days and had gained rapidly in weight and strength, there was found a definite tenderness of the muscles in the posterior triangle on the left side of the neck and two distinct tender nodules just behind the pos-terior margin of the sternomastoid muscle. One of these tender nodules, thought to be a lymph-gland, and a portion of the deeper layers of the muscle were excised. One-half of these tissues were immediately emul-sified for cultures and the other half fixed in formalin-Zenker for sec-tions. The excision of the fascia and muscle precipitated another violent attack of pain and spasm of the muscles of the left side of the neck. The cultures in tall columns of ascites plain broth of the emul-sion of muscle showed a pure culture of a short-chained streptococcus, and those from the thickened fascia, streptococci and staphylococci.

Blood-agar plates from the culture in ascites plain broth from the

tooth-pulp and from the muscle (injected into animals) showed pure cultures of streptococci producing a narrow, hazy zone of hemolysis.
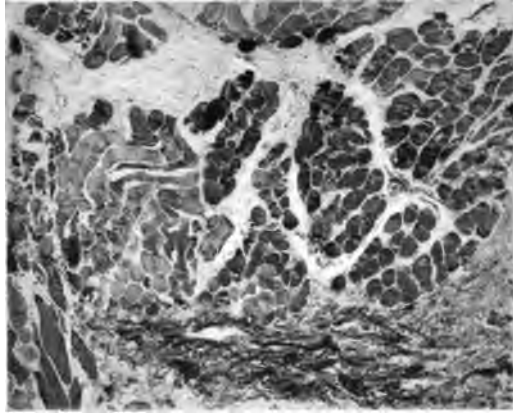
Fig. 25.—Section of the muscle excised from the left side of the patient's neck.   Note the marked infiltration by connective tissue, the irregular staining, and the atrophy of muscle-fibers.   Hematoxylin and eosin (× 60).

It was thought that this streptococcus might be present quite generally on the mucous membrane in this patient.   Cultures from the nose and pharynx and three out of six cultures from the stool proved that this was actually the case.

Sections of the excised muscle showed marked increase in the interstitial tissue, poorly staining nuclei of adjacent muscle-fibers, and slight round-cell infiltration (Fig. 25).   Sections of the fibrous nodule and fascia showed old and young connective tissue, absence of lymphoid tissue, small nests of round-cells, plasma cells, and erythrocytes, chiefly around blood-vessels.   Gram-Weigert and methylene-blue stains for bacteria revealed a moderate number of diplococci in or adjacent to the fibrous tissue between the muscle-fibers and nests of cellular infiltration (Fig. 26) and a large number within and surrounding a small-sized blood-vessel in the center of the fibrous nodule (Fig. 27).

Fig. 26.—Diplococci, single and in short chains, and two leukocytes in tender fibrous node in the deep fascia from the left side of the neck.   Methylene-blue and eosin (× 1000).

A vaccine was prepared by heating the streptococci suspended in salt solution from the primary cultures of the pulp of the tooth and muscle and treating it with equal parts of the patient's serum for two hours at 37° F. and over night in the ice-chest. This was used in the treatment of the patient. The first dose consisted of 25,000,000, and was followed by marked muscle pains, especially at the left side of the neck, nausea, extreme exhaustion, and slight fever. The subsequent injections were at first diminished and then gradually increased, the aim being to give a distinct but not severe reaction following the injection. Dr. Grimes, who referred the patient to me, reported, three months after the extraction of the tooth, that the patient has shown gradual improvement; the attacks are milder and of shorter duration, the intervals between attacks are longer, and there has been marked improvement in the general nervous tone.

ANIMAL EXPERIMENTS

Intravenous injections were made into rabbits, guinea-pigs, and dogs, and intraperitoneal injections into mice. The streptococcus as isolated from the pulp of the tooth was injected into 4 rabbits, 2 guinea-pigs, and 2 white mice, all of which recovered. The primary culture after one animal passage

Fig. 27.—Diplococci within the lumen and in the wall of the blood-vessel and within the leukocyte just outside of the blood-vessel in the center of the tender fibrous nodule of the deep fascia from the left side of the neck. Gram-Weigert (× 1000).

was injected into 2 rabbits, 1 dog, and 2 mice. The rabbits and dog recovered; the mice died. Thirteen animals were injected. In 10 of these circumscribed hemorrhages and edema opposite the roots of teeth or at the foramina of exit of the superior or inferior maxillary nerves were easily visible; in 7 there were lesions of the muscles, 4 of which were limited largely to the muscles of the left side of the neck; in 6 there were lesions of the pulp of the teeth and the superior or inferior dental nerves; in 3 there were insignificant lesions of the kidney, in 2 lesions in the gallbladder, and in 1 lesions in the stomach. The spleen, adrenal, endocardium, vagus, and sympathetic ganglions and subcutaneous nerves were normal. No lesions were found in the nerves supply-

'16—3

ing hemorrhagic muscles. The diphtheroid bacillus did not produce
lesions in the one rabbit and one mouse injected.

The streptococcus from the muscle in the first and second cultures
was injected into 2 rabbits, 1 guinea-pig, and 1 mouse, producing lesions
of the muscles, chiefly of the neck and shoulders, in all. In the rabbits
there were also hemorrhage and infiltration of the dental nerves, and
gross lesions in the dental pulps and periosteum opposite the roots of the
teeth. In 1 there were a few hemorrhages of the stomach, in the other,
hemorrhages of the kidney; in the mice there was a mild peritonitis.

To the portion of the above cultures of streptococci left over and hav-
ing marked affinity for the muscles was added 0.5 per cent. formalin.
This was allowed to stand over night at room temperature, a portion being
put aside for direct injection; the rest was centrifugalized and the bacteria
washed in Ringer's solution. The former was injected intravenously
into a rabbit in amounts of 10 c.c. on four occasions over a period of
eleven days. The rabbit showed a moderate number of small hemor-
rhages in the muscles of the hips and shoulders and a few in the stomach.
The washed suspension was injected one month later into three rabbits,
each receiving the growth from 150 c.c. of the broth cultures. All died
in twenty-four hours. The muscles in all had a boiled appearance, and
those about the shoulders, neck, and spine had large and small hemor-
rhages associated with edema; two had, in addition, a hemorrhage of
the pulp of the teeth; and one a few hemorrhages about the joints, in
the tricuspid valve, and in the left inferior dental nerve. The lungs were
free from hemorrhages.

Two cubic centimeters, or approximately 500,000,000 of the heat-
killed streptococci, failed to produce lesions, but this may have been due
to the small size of the dose. The filtrate of the formalinized cultures
failed to produce lesions in the muscles following three injections of
10 c.c. each into one rabbit. Three injections into one rabbit, over a
period of eleven days, of the slightly hemolyzing streptococcus from the
pharynx were followed by moderate numbers of lesions in the muscles
in the right side of the neck, the right elbow, and right shoulder and in
the intercostal muscles. The streptococcus from the stools in the second
culture did not produce lesions. The living streptococci from the tooth,
muscle, pharynx, and stool in the first or second cultures, and after one
animal passage, and the heat or formalin-killed streptococci were injected
altogether into 24 animals (15 rabbits, 3 guinea-pigs, 1 dog, and 5 mice).
Of these, 17 (71 per cent.) showed myositis, 13 (54 per cent.) lesions of

the periosteum opposite teeth or at nerve foramina, 12 (50 per cent.) lesions of the pulp of teeth, and 10 (42 per cent.) lesions of the dental nerves.* Similar results have been obtained since in 2 cases of myositis and arthritis with streptococci isolated from the diseased pulp of extracted teeth.

Previous to these experiments lesions of the pulp of teeth and the dental nerves were not usually looked for, but recently careful search for similar lesions in these structures has been made in numerous animals injected with streptococci from other sources. In three instances only were there found lesions of the pulp of teeth and dental nerves. Two of these animals showed myositis in addition. The details in the following experiments will serve to illustrate specifically the results obtained:

RABBIT 656.—Belgian hare; weight, 1510 grams. January 19, 1916, injected intravenously with the growth from 30 c.c. of ascites-dextrose-broth of a pure culture of streptococcus from the pulp of the extracted tooth.

January 20: Seemed quite ill; respirations were accelerated; appeared to have pain in walking and promptly crouched when quiet. The hair was roughened and there was marked lacrimation of the left eye, but no swelling of the face.

January 21: Seemed much better; was more active, but tremulous, and appeared nervous. There was lacrimation of the left eye, and an easily recognizable swelling of the left side of the face (Fig. 28). Slight pressure over this area appeared to cause pain, and the swelling could be easily felt. Chloroformed. A rather large number of linear hemorrhages in the skeletal muscles, chiefly in the tendinous portions of the flat muscles of the shoulder and deeper muscles of the left side of the neck and of the front extremities, were found. There were no lesions of the muscles of the hind extremities, the dorsal and lumbar regions of the spine, nor of the intercostal muscles and diaphragm. On removing the skin on the left side of the face, marked edema, infiltration, and hemorrhage of the subcutaneous tissue, the fascia, the muscles, and the periosteum were found. The hemorrhages in the periosteum opposite the molars appeared to be the center of the edematous area. The hemorrhagic infiltration extended to the under surface of the orbit. The pulp of the left third and fourth upper molars was found to be edematous and hemorrhagic. The hemorrhages were small and punctate, and were not found in the pulp of the two corresponding teeth on the opposite side. On dissecting away the soft tissues of the lower jaw it was found that hemorrhages of the periosteum had occurred opposite

* The incidence of the lesions in the other organs corresponded with that given in my paper, "Elective Localization of Streptococci," Jour. Amer. Med. Assoc., 1915, xlv, 1687-1691.

the apices of the right lower incisor, the first and two last molars, and the second left lower molar, and surrounding the right mental foramen. These lesions were similar to those shown in Fig. 30. The pulp of the teeth surrounded by hemorrhages in the periosteum was found to be edematous and hemorrhagic, whereas three adjacent pulps appeared normal. The

Fig. 28.—Rabbit 656 showing marked lacrimation of the left eye and swelling of the left side of the face forty-eight hours after the intravenous injection of the streptococcus from the pulp of the extracted first upper left molar.

left superior dental nerve was extremely hyperemic, and a number of small hemorrhages were found in the sheath. The only lesions of the viscera were three small hemorrhages in the mucous membrane of the pyloric end of the stomach and three small subserous hemorrhages at the fundus of the gallbladder.

January 23: Blood-agar plate cultures of the blood produced 1 colony of streptococcus and those of the emulsions of the pulp of teeth, 5 and 18 colonies respectively. Cultures in ascites-dextrose broth from the emulsions of the pulp of two teeth, of the hemorrhagic muscle, of the edematous tissue over the jaw, and of the hemorrhagic periosteum, showed a short-chained streptococcus.

Sections of the edematous tissue over the left jaw showed extreme hemorrhage, edema, and beginning leukocytic infiltration. In the pulp of two teeth from which sections were made were large and small hemorrhages, chiefly beneath the layer of odontoblasts, and in the left superior dental nerve were small areas of hemorrhage in the sheath. Sections of hemorrhagic areas in the scapular muscles showed marked hemorrhage

Fig. 29.—Diplococcus in an area of hemorrhage in the left superior dental nerve of rabbit shown in Fig. 28. Gram-Weigert (× 1000).

between the muscle-fibers, separation and fragmentation of the latter, and slight leukocytic infiltration. Gram-Weigert stains showed diplococci

Fig. 30.—Left lower jaw of Rabbit 659 injected three days previously with 5 c.c. of twenty-four-hour tissue-ascites-fluid culture of the streptococcus from the tooth. Note the edema and hemorrhage in the periosteum opposite the root of the canine and surrounding the inferior dental nerve at the foramen of exit (× 2).

in or adjacent to the hemorrhagic areas in the edematous periosteum, in the muscle from the scapula, in the pulp of the teeth, and in the left superior dental nerve (Fig. 29).

Fig. 31.—The pulp of the inferior canine and inferior dental nerve from Dog 412 two days after an intravenous injection of the streptococcus isolated from the hemorrhagic pulp of the second upper left molar. Note the numerous large and small hemorrhages in the pulp of the left lower canine and nerve (× 2).
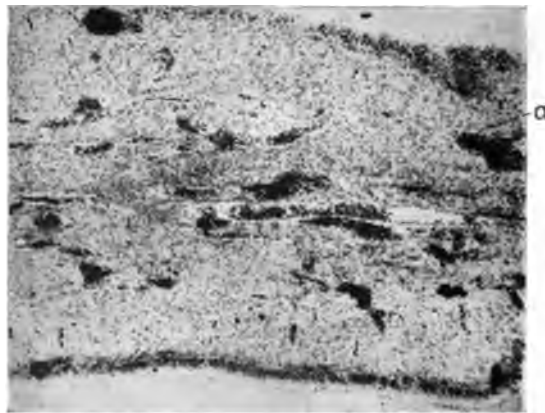
Fig. 32.—Section of the pulp of the left lower canine shown in Fig. 31. Note the marked hyperemia and the large and small hemorrhages. Hematoxylin and eosin (× 60).
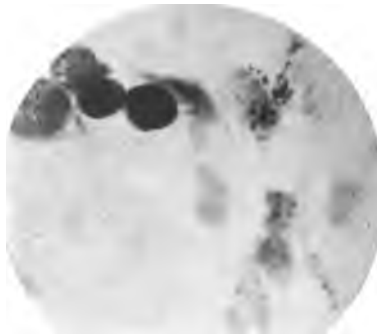
Fig. 33.—Diplococci, single and in short chains, within and outside of leukocytes adjacent to the area of hemorrhage at a in Fig. 32.

Dog 412.—A white and black dog; weight, 9.5 kilos. January 22, injected intravenously with the growth from 90 c.c. of ascites-dextrose broth of the streptococcus from the hemorrhagic pulp of a tooth of Rabbit 656.

January 24: Seemed well; was active; no swelling of the face; no tenderness over joints or muscles. Chloroformed. The left inferior

Fig. 34.—Section through the hemorrhagic area in the left inferior dental nerve, shown in Fig. 31. Note the marked edema and large and small hemorrhages and leukocytic infiltration of the sheath. Hematoxylin and eosin (× 60).

Fig. 35.—Diplococci and double chain of streptococci in the hemorrhagic and infiltrated area, *a*, in the sheath, shown in Fig. 34.

dental nerve was found to be edematous and hyperemic and contained a number of large and small punctate hemorrhages (Fig. 31). The pulp of the corresponding canine tooth likewise appeared edematous and contained numerous punctate hemorrhages. The corresponding nerve and pulp on the opposite side appeared normal (Fig. 31). There were similar but less marked lesions of the left superior dental nerve and pulp of the

canine tooth. The first upper and lower molars were examined, but only the first left lower molar showed unmistakable hemorrhage. The muscles were free from visible lesions except for a few hemorrhages in the flat muscles under the scapulas. In a painstaking examination of all the organs no other apparent lesions were revealed.

Fig. 36.—Section of the dental pulp of the left upper molar of Guinea-pig 141 injected two days previously with the streptococcus from the pulp of the patient's tooth. Note the marked leukocytic infiltration and hemorrhage. Hematoxylin and eosin (× 240).

Fig. 37.—Diplococcus in infiltrated area *a* shown in Fig. 36. Gram-Weigert (× 1000).

January 25: Blood-agar slants made from the blood were sterile.

Sections for microscopic study were made from the left inferior dental nerve, from the pulp of the teeth mentioned, and from the superior maxillary nerve. Hemorrhages and beginning leukocytic infiltration were found in the pulp of the left inferior canine (Fig. 32), and a small

number of hemorrhages in the pulp of the first left lower molar, but practically none in the others. These hemorrhages were most numerous immediately beneath the layer of odontoblasts and at the distal portion of the pulp (Fig. 32). Sections of the left inferior dental nerve showed marked edema, a moderate leukocytic infiltration, and a number of large
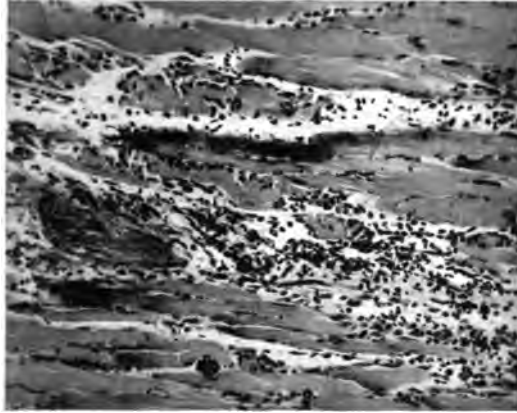
Fig. 38.—Section of the left triceps of Guinea-pig 155 injected two days previously with the streptococcus from the muscle of the patient. Note the marked hemorrhagic and leukocytic infiltration and separation of muscle-fibers. Methylene-blue and eosin (X 140).

Fig. 39.—Diplococcus in infiltrated area shown in Fig. 38. Gram-Weigert (X 1000).

and small hemorrhages, chiefly in the sheath (Fig. 34). There were no lesions in the left superior maxillary nerve. Gram-Weigert and methylene-blue stains for bacteria showed scattered diplococci and at times chains of diplococci in and adjoining the hemorrhagic areas (Figs. 33 and 35). In one instance a mass of diplococci surrounded by erythro-

cytes was found just outside the wall, and two diplococci in the wall of a small blood-vessel. In a number of instances the diplococci were found within leukocytes and in what appeared to be endothelial cells. No bacteria could be found in the normal portions of the pulps and nerves showing lesions, nor in those free from lesions.

GUINEA-PIG 155.—White guinea-pig; weight, 320 grams. February 19, injected intravenously with the growth from 30 c.c. of ascites-dextrose broth of the streptococcus isolated from the muscle of the patient.

February 21: Seemed quite well, but appeared to be muscle-sore. Chloroformed. Numerous small hemorrhages associated with edema in the triceps muscles, a moderate number in the muscles of the left shoulder, and a few hemorrhages in the deeper layer of the muscles of the left side of the neck were found. There were no lesions of the dental

Fig. 40.—Section of the left trapezius of Rabbit 660 forty-eight hours after intravenous injection of the streptococcus from pulp of the left upper molar of rabbit shown in Fig. 28. Note the marked edema, leukocytic infiltration, hemorrhages, and the disintegration of the muscle-fibers. Hematoxylin and eosin (× 120).

nerves, but the pulp of the two left upper molars was extremely hyperemic and contained distinct hemorrhages. There were no other findable lesions.

February 24: Cultures from the blood in ascites-dextrose broth were sterile.

Sections through the areas of hemorrhage in the scapular muscle showed marked extravasation of blood-corpuscles, leukocytic infiltration, separation and necrosis of muscle-fibers (see Fig. 38, illustrating similar lesion in triceps muscle). Sections of the pulp of the left first upper molar showed a number of small hemorrhages, while in those of the superior maxillary and right superior dental nerve there were no lesions. Gram-Weigert and methylene-blue and eosin stains showed a few scattered diplococci in the hemorrhagic and infiltrated area in the muscle and adjacent to the hemorrhages in the tooth-pulp (Fig. 39).

THE STREPTOCOCCUS

The streptococcus isolated from the dead pulp of the tooth, the muscle, the pharynx, and the stool, produced small, round, slightly elevated, grayish-brown, non-adherent, rather dry colonies on aërobic blood- (human) agar plates.   In broth it produced a diffuse turbidity with a small amount of flocculent sediment at the end of forty-eight hours.   It acidified and coagulated milk.   In liquid media it grew in short chains and diplococci.   In many instances the single members of the diplococci were quite round and resembled staphylococci.   The strains from the tooth and muscle were freely susceptible to phagocytosis, and the virulence was of a low order.   The streptococci from blood-agar slants in salt solution used as a vaccine resisted 60° C. for thirty minutes on consecutive days, while after the third heating the subcultures remained sterile.   The blood of the animals soon became sterile, and nearly all recovered promptly from the effects of injection.   The organism resembled very closely the streptococci that I have isolated from other cases of myositis and strains from other sources having affinity for muscles.

In the table is given the fermentative power of the strains isolated from the pulp of the tooth, the muscle, the pharynx, and the stool. It is seen here, as has been found to be the case with other streptococci, that there is little parallelism between pathogenicity and the degree or range of fermentative powers.

FERMENTATIVE POWERS OF THE STREPTOCOCCUS*

STREPTOCOCCUS	DEXTROSE	LACTOSE	SACCHAROSE	MALTOSE	RAFFINOSE	MANNITE	SALICIN	INULIN
Tooth-pulp...............	2.4	1.5	0.9	1.9	0	1.3	2.0	0
Pharynx..................	1.9	1.8	0	1.6	1.8	1.0	0	0
Muscle..................	1.5	1.2	1.5	1.3	0	0	0	0
Stool....................	2.9	2.3	1.1	3.2	0	0	2.3	0

SUMMARY

A streptococcus having peculiar properties was isolated from the dead pulp of the left upper first molar in the region where the attacks

* The standard sugar-free broth containing the usual amounts of the various carbohydrates was used in the fermentation tests.   The cultures were incubated seventy-two hours.   The figures indicate the number of cubic centimeters of normal tenth sodium hydroxid required to neutralize 5 c.c. of the broth culture, phenolphthalein being used as the indicator.

of pain usually began. The streptococcus was also demonstrated in the sections and isolated from the infiltrated deep fascia and muscles of the left side of the neck. A similar streptococcus was isolated from the pharynx and stool. This streptococcus was proved to have elective affinity for the pulp of teeth, dental nerves, and muscles in animals. It was repeatedly isolated from and demonstrated in the experimental lesions in animals whose blood was sterile; the lesions were again produced on reinjection and the streptococcus again isolated. Many animals appeared to be in pain and one rabbit (Fig. 28) had marked swelling and tenderness over the left upper jaw. This affinity was proved absent in the diphtheroid bacillus and Bacillus fusiformis, which also were isolated from the pulp of the tooth, and in the streptococcus broth culture filtrate. Streptococci from other sources rarely cause lesions in the pulp of teeth and dental nerves. The phagocytic power of the patient's blood following the attack over the strain from the tooth was twice that of comparable normal blood.

These results would appear to warrant the conclusion that the attacks of pain in the face in this patient were due to a streptococcus infection of the sheaths of the dental nerves, and that the pain, swelling, tenderness, and spasm of the muscles of the neck were due to myositis and fibrositis—the result of infection by this streptococcus. The demonstration of living streptococci in the pulp of the tooth and in the fascia and muscle during quiescent intervals is significant and may explain the recurrence of the attacks. The cavity in the tooth containing the dead pulp, which was originally infected from the mouth, judging by the character of the filling and of the bacterial flora, was quite unable to heal, for mechanical reasons. The contents of the cavity appeared to afford a culture-medium for the growth of the streptococcus. By stimulation of the defensive mechanism in the patient during the attacks active growth appeared to be held in check and the symptoms disappeared in consequence, only to reappear later from recurrence of active growth and localization of the streptococci when the immunity was low.

The improvement in the patient since extraction of the tooth appears to be due to the removal of this focus and to prolonged artificial stimulation of the defensive mechanism by means of the autogenous vaccine, which, it is hoped, will lead to the destruction of all the streptococci in the muscle and dental nerves, and result in ultimate recovery. However, the isolation of this streptococcus from so many places indicates that complete recovery will probably be difficult.

THE CAUSATION OF GASTRIC AND DUODENAL ULCER BY STREPTOCOCCI *

EDWARD C. ROSENOW

Lesions of the stomach have been produced experimentally by excision; by tying a fold of mucous membrane with a string; by local application of the cautery, and of corrosive chemicals, such as silver nitrate and nitric acid;[1] by the introduction of very hot gruels;[2] by the submucous injection of silver nitrate,[3] nitric acid, adrenalin, alcohol,[4] and gastrotoxic serum;[5] and by the injection of lead chromate[6] and fat[7] into the gastric artery; but since these lesions heal promptly in from five to twenty-one days, according to their severity,[1, 2, 6] and since the methods used are so different from what occurs naturally, valuable though the results are in one respect or another, they have little bearing on the problem of ulcer of the stomach in man.

The hemorrhages, erosions, and ulcerations observed during severe intoxication following systemic injections of snake-venom, pilocarpin, atropin, chloroform, phenol, copper sulphate,[8] bile and bile salts,[9, 10] β-tetra-hydronaphthylamin,[11] adrenalin,[12] diphtheria toxin,[13, 14] and culture filtrates of various bacteria, while having some parallelism in acute ulcer during severe or fatal intoxications or infections, have little bearing on the problem of the usual ulcer of the stomach in man.

The same may be said of the lesions of the stomach which develop commonly in animals during the moribund condition following adrenalectomy.[15, 16, 17, 18, 19, 20]

Ulcer of the stomach has been produced by interference with its nerve supply (hence the blood supply), by section either of the vagus or of the sympathetic nerves, or of both, and by section of the spinal cord.[21, 22, 23, 24] Most observers, however, have obtained only doubtful results in this field. The studies of Vedova[22] and Durante[23] merit special

mention. They have shown that in dogs and rabbits ligation or section of the sympathetic nerves is followed somewhat regularly by acute ulcer of the stomach. In some instances they have observed ulcers which were chronic in type, but not in time, the animals surviving the operation for a short time only. The lesions in the stomach were due, according to Durante, to spasm of the blood-vessels as the result of an overproduction of adrenalin, the adrenals showing marked congestion and hemorrhage following ligation of the splanchnic nerves. But since there is no evidence of increased adrenal function, as manifested especially by an increased blood-pressure, in patients with ulcer, and since the death of the animals occurred as a result of the method employed, it is difficult to see how these results, suggestive as they are, can be applied, for in ulcer the interference with the nerve supply of the stomach is necessarily slight.

The infectious origin of ulcer, while not generally accepted, has had adherents for many years. Experimentally, ulcer has been produced by intravenous injections of the pyocyaneus bacillus,[25] the dysentery bacillus,[26] the lactic-acid bacillus,[27] and the colon bacillus.[28, 29, 30]

Ulcer was found to occur as a part of a general pyemia following intravenous injections—(1) of pus by Lebert[31] (1857) and by Cohn[32] (1860), (2) of streptococci and staphylococci by Letulle,[33] and (3) of pneumococci by Bezançon and Griffon.[34] It is a well-known fact that ulcer of the stomach in man occurs not infrequently during severe or fatal infections of various kinds, particularly streptococcal infections.[35, 36, 5] Bacteria have been repeatedly demonstrated in the edges and floors of ulcers—Boettcher,[37] in 1874, being the first to do this—but these have usually been considered secondary invaders. Dudgeon and Sargent[38] isolated a diplostreptococcus from the edges of the ulcers and from the peritoneal exudate in 4 of 9 cases of peritonitis following perforation. The peritonitis was of a mild grade, corresponding to the low virulence of the strains isolated. Hutyra and Marek[39] state that ulcer of the stomach is found in domestic animals dead from "catarrhal fever" and in purpura hæmorrhagica. Bolton[5] states that probably the commonest cause of necrosis of the mucous membrane and resulting acute ulcer of the stomach is bacterial infection, that the infection occurs through the blood-stream, and that the necrosis is due to the direct effect upon the tissues of the bacterial posion, alone or together with the gastric juice. Letulle reports a case of ulcer following chronic abscess of the maxillary antrum, and notes the occurrence of

acute ulcer in other cases in which there were local septic foci. This raises the important question, to quote Bolton, "whether many cases of simple acute ulcers owe their origin to some local septic focus which is so commonly unrecognized or unheeded." Recently numerous observers have emphasized the etiologic relation of focal infection to ulcer of the stomach.

In 1913 I reported[40] some experiments which showed that streptococci, quite irrespective of their original source, when of a certain grade of virulence, exhibit affinity for the gastric mucous membrane, producing a localized infection and ulcer. The report at that time was summarized as follows:

Intravenous injection of streptococci of the proper grade of virulence may be followed by ulcer of the stomach and duodenum. The ulceration is due to a localized infection and secondary digestion. The ulcers are usually single and deep, with marked tendency to hemorrhage and perforation, and in many respects resemble gastric ulcer in man. When we take into consideration this close resemblance, the fact that injection of streptococci which have grown in tonsils produces the lesions, and that the virulence of the germs when the affinity for the stomach is greatest is of such a character that a general infection does not occur, it appears altogether reasonable to suppose that in man gastric ulcer may be caused by streptococci also. The supposed relation between infected tonsils or gums and gastric ulcer may be due not to the swallowing of bacteria, as is usually supposed, but to the entrance into the blood of streptococci of the proper kind of virulence to produce a local infection in the wall of the stomach. Many other observations might be cited, such as associated infections of the gallbladder and appendix, which suggest that gastric ulcer may be due to streptococci.

Before it could be accepted, however, that the usual ulcer of the stomach in man is due commonly to a local hematogenous streptococcal infection, it was necessary to show, first, that in this type of ulcer these organisms are commonly present to the exclusion of other bacteria; and second, that the streptococci isolated from the ulcer wall, as well as those from foci of infection in patients having ulcer, produce, when injected into animals under otherwise normal conditions, ulcers of the stomach and of the duodenum resembling those in man.

By the use of a special technic the first requirement has been covered and reported.[41] Streptococci have been demonstrated in the tissue or isolated in cultures (often in pure form) in 42 of 54 typical chronic ulcers in man. The second requirement, as I have pointed out recently,[42]

has also been fulfilled.   I wish now to give in greater detail the results
of my experiments.

TECHNIC

The technic of making cultures from ulcer is described in another
paper.[41]   In collecting material for cultures great effort was made to
obtain bacteria from the depths of the foci of infection with as little
surface contamination as possible.   This is of great importance.   The
bacteria for injection were grown in tall columns (12 cm.) of ascites-
dextrose broth at 35° to 37° C., for from eighteen to twenty-four hours,
centrifugalized, the clear broth poured off, and the bacteria suspended
in salt solution so that 1 c.c. of the suspension contained the growth
from 15 c.c. of the broth culture.   Blood-agar plate cultures and
smears were made of the material obtained directly from the ulcer
or the focus, from the broth cultures, and from the suspensions imme-
diately before injection, to determine the viability and identity of
the organisms present.

In some instances small doses of the broth culture and cultures from
blood-agar slants were injected.   Bacteria from the ulcers, when in-
jected into animals, were usually in the second culture, from single
colonies (from two to seventy-eight days old) in the original shake
cultures.   In the case of strains from foci of infection, the bacteria
used for injection were usually from the primary culture, from eighteen
to forty-eight hours after the inoculation of material from the focus
directly into tall columns of ascites-dextrose broth.   The broth culture
filtrates were injected in some instances to determine the presence
or absence of an ultramicroscopic virus.   They showed only a slightly
greater tendency to produce lesions in the stomach than did filtrates
from other streptococcus cultures.

In the case of the animals, routine cultures were made from the
blood (0.5 c.c.), the joint fluid (usually from two or more joints), the
bile, and from emulsions of the ulcers, of the areas of hemorrhage, and
often from the adjoining normal mucous membrane.   Cultures from
various other tissues and from the blood at intervals during life were
made in selected instances.   The technic for tissue cultures from animals
was similar to that employed in making cultures from ulcers from
patients.

No special attention was paid to the diet of the animals.   The
injections were made usually in the latter part of the day, some hours
after the feeding period.   Except for feeding experiments, and the local
and intraperitoneal injections of the streptococci, the bacteria were
injected intravenously, the injections being made rather rapidly through
a fair-sized needle (23 gage).   It was the rule to inject at least two
animals with a given strain, one receiving a small dose, the other a
larger dose.   Because of the low virulence of the strains the dose was
relatively large, consisting in the main (for rabbits and dogs) of the

growth from 5 to 25 c.c. of the broth culture per kilo of weight. In special instances much smaller doses sufficed to produce ulcer.

For sections the tissues from the ulcers in man and from experimental ulcers were fixed in 10 per cent. formalin or in Zenker's fluid, embedded in paraffin, and stained chiefly with hematoxylin and eosin, methylene-blue and eosin, or with neutral gentian. The Gram-Weigert method was used as a routine for the staining of bacteria, care being exercised not to decolorize the sections further than to a pale blue.

REVIEW OF CASES AND EXPERIMENTS

CASE 773.—A man, fifty-three years of age, with typical symptoms of duodenal ulcer of three years' duration, was operated on by Dr. Bevan October 27, 1913. There was excised a hard, indurated, much thickened, and adherent duodenal ulcer, which was perforating against the gallbladder. Cultures were made at once. Smears from the emulsion showed a few Gram-staining cocci and diplococci. The cultures yielded fully 1500 colonies of staphylococci and approximately 20 colonies of a short-chained, non-hemolyzing non-adherent streptococcus.

The streptococcus (Fig. 41), as isolated, was injected into two dogs and two rabbits. The dog receiving the large dose died in forty-eight hours, showing marked distention of the stomach with gas containing a large amount of carbon dioxid, and hemorrhages of the mucous membrane of the stomach with ulceration in two areas. The other dog thirteen weeks later died of distemper. It showed one round, deep, sharply circumscribed, somewhat indurated ulcer of the duodenum, 5 mm. in diameter, 2 cm. beyond the pyloric ring (Fig. 47). The floor of the ulcer in the center consisted only of the thickened and adherent peritoneal coat. No other lesions could be made out. One rabbit developed one ulcer in the pylorus, together with myositis and beginning endocarditis. The other did not show lesions of the stomach, but there were focal nephritis and myocarditis.

Fig. 41.—Smear from a twenty-four-hour ascites-dextrose broth culture of the streptococcus isolated from a duodenal ulcer in man (Case 773). Gram-Weigert stain (× 1200).

The staphylococci failed to produce lesions of the stomach, but produced a focal nephritis, and, in one rabbit, cholecystitis.

The feeding of a large amount of cultures of these strains mixed with chopped meat and particles of dried splintered bone, failed to produce lesions in the stomach or duodenum in the three dogs so treated.

After one animal passage, the streptococcus produced acute ulceration of the stomach in a rabbit, and a chronic ulcer causing death from hemorrhage in the only dog injected (Dog 41).

After two animal passages, the streptococcus was injected into two dogs. One developed three hemorrhagic ulcers,—two in the duodenum and one in the pyloric end of the stomach,—cholecystitis, pancreatitis with fat necrosis, enteritis, and myocarditis. The other dog developed no lesions of the stomach or duodenum, but showed fatty degeneration of the liver and ulcerative colitis.

After three animal passages the streptococcus produced two ulcers of the stomach in one of two dogs injected, together with enteritis and

Fig. 42.—Smear from a twenty-four-hour ascites-dextrose broth culture of the streptococcus isolated from an infected tooth in a patient with ulcer of the stomach. The smear was made at the time that the strain was proved to have affinity for the stomach in animals (Case 52). Gram stain (X 1200).

colitis, and intussusception of the ileum into the cecum. Cultures from the blood of these dogs yielded both non-hemolyzing and hemolyzing streptococci. The non-hemolyzing strain in the next passage produced no lesions of the stomach in the three rabbits injected; one rabbit developed arthritis and another cholecystitis; the hemolyzing strain likewise produced no lesions of the stomach, but caused a suppurative arthritis in two rabbits and one dog. The dog showed what appeared to be a phlegmonous gastritis, but no ulceration.

After five animal passages the non-hemolyzing strain was injected into three guinea-pigs, two dogs, and one rabbit. All but two of these animals showed hemorrhages in the lungs. The rabbit and the dogs

showed hemorrhages of the gallbladder and mild arthritis. In one dog there was marked degeneration of the liver. Cultures from the joint fluid in these were negative. Cultures from the livers which showed no gross changes remained sterile, while those from the liver in which there was degeneration yielded a large number of streptococci.

Dog 41.—Injected November 11, 1914, with the growth from 150 c.c. of a dextrose broth culture of the streptococcus after one animal passage. Cultures from the blood the day after injection were negative.

November 25: Dog seemed well, but had lost in weight and was less active than usual.

January 3: Died at 9 A. M., fifty-three days after a single injection. Emaciation; tissues everywhere pale; hemoglobin, 30 per cent.; blood remained unclotted for thirty minutes. There were one small, round, deep ulcer with elevated and indurated margins and hemorrhagic base, which extended through the mucous membrane; one healing ulcer in the stomach and one in the duodenum; and one active infected ulcer 1 cm. beyond the pyloric ring (2 by 5 mm.). The margins of the latter were infiltrated and opaque, and the peritoneum opposite showed thickening and adhesions. The liver disclosed fatty infiltration and localized fibrous myocarditis. The other organs revealed no changes. A Weber test for occult blood in the dark-brown contents of the lower bowel was strongly positive.

Cultures from blood, joint fluid, and kidney remained sterile, while those from bile yielded 15 colonies of non-hemolyzing streptococci.

Dog 37.—Injected intravenously November 3, 1913, with the growth from 280 c.c. of a dextrose broth culture of the streptococcus in its second culture.

November 7: Cultures from blood gave the streptococcus injected.

November 16: Growth from 120 c.c. injected intravenously.

November 19: Culture from blood made the day after injection yielded streptococci.

November 28: The dog had grown thin and did not eat with a relish, but otherwise seemed fairly well.

February 13: Found dead from distemper. There was an acute pneumonia and pleuritis. The stomach was normal—no scars indicating healed ulcers could be made out. In the duodenum, 2 cm. from the pyloric ring, there was a round, deep, sharply circumscribed ulcer, 5 mm. in diameter (Fig. 47). The margins were undermined and adherent to the muscular layer. The floor in the center consisted of the thickened and adherent peritoneal coat.

Sections showed marked invasion of the muscular coat by connective tissue and thickening of the peritoneal coat (Fig. 48, *a* and *b*). The mucous membrane at the margin of the ulcer revealed round-cell infiltration in areas at the juncture of the uninvolved portion. The mucous

glands evinced little change. No thrombosed blood-vessels could be made out. A search for bacteria revealed a few diplococci (Fig. 49).

CASE 779.—Chronic ulcer of the stomach in a woman forty-three years of age. The symptoms of ulcer had been present for twelve years. She had had the usual periodic attacks of exacerbation and remissions, and was finally operated on by Dr. Ochsner October 29, 1913. There was an indurated, crater-like ulcer, 3 cm. by 1 cm., at the pyloric end of the stomach. The pylorus and the lymph-gland draining the area were removed and cultured. The margin and base of the ulcer were indurated, the base clean and smooth. The mucous membrane was adherent and not undermined. The ulcer appeared to be healing.

Smears from the base of the ulcer showed leukocytes, epithelial cells, yeast-cells, and Gram-positive cocci, mostly within leukocytes.

October 30: Cultures from emulsion of the ulcer, made after the surface was sterilized, yielded approximately 180 colonies of small cocci, which appeared singly and in masses, and approximately 50 colonies of a short-chained streptococcus, while those from the lymph-gland gave five colonies of the streptococcus. Control cultures from the adjacent normal mucous membrane were negative except for a few colonies of staphylococci and aërobic saprophytic bacilli.

November 4: Subcultures of eight colonies of the small, Gram-positive streptococcus from the ulcer and of three of those from the node, yielded small, grayish, non-hemolyzing, non-adherent colonies on blood-agar plates, and short chains in ascites-dextrose broth identical with those found in Case 773 (Fig. 41).

The streptococcus in second culture was injected into one rabbit and one dog. The mucous membrane of the rabbit did not show lesions at the end of one week, while that of the dog, four months after the injection, showed a scar indicating a healed ulcer near the pyloric ring. After the streptococcus had undergone one animal passage, the following experiment was made:

DOG 42.—Injected intravenously, November 7, with the growth from 150 c.c. of an ascites-dextrose broth culture of the streptococcus isolated from the blood of the dog mentioned.

November 8: Ill, lay quiet, did not eat. There was no tenderness or swelling of the joints.

November 11: Ill. Chloroformed and examined at once. In the stomach were numerous small (1 to 5 mm.) and large (1 to 3 cm.) hemorrhagic areas, areas of necrosis, erosions, and ulcerations (Fig. 43). The lesions were more numerous in the fundus, but larger in the pylorus. The intervening mucous membrane, except for slight congestion, was normal, as was that of the duodenum. The stomach-contents, free from food, were strongly acid in reaction and contained a small amount of altered blood. The mucous membrane of the small and large intestines was congested.

Sections through two areas of hemorrhage and ulceration in the cardiac end of the stomach showed extravasation of blood, which was most marked as the surface of the mucous membrane was reached. This was true in practically all the areas of hemorrhage. In one there was distinct ulceration. The ulcerated area was covered in places by a thick layer of necrotic cells, numerous leukocytes, blood-corpuscles, and fibrin. The mucous membrane beneath this layer presented an interesting picture. There were, first, a dense layer of polymorphonuclear leukocytes, then a layer in which there was marked hemorrhage with less leukocytic infiltration, and then the more normal gland structure, throughout which were found leukocytes in large number (Fig. 44). The chief cells showed marked degeneration; the protoplasm was granular, the nuclei fragmented, with marked desquamation. The eosin-staining parietal cells, on the other hand, appeared normal, even where all the chief cells had disintegrated and desquamated. Some of these retained normal staining properties and position, even where they had been detached from the acini (Fig. 45). The other coats were unchanged. The blood-vessels in the submucosa were dilated, and a number of veins showed rather marked mural implantation of leukocytes, appearing as a beginning thrombosis (Fig. 44). Search for bacteria revealed few diplococci in the deeper layers, but masses of diplococci and short chains beneath the sloughing necrotic layers, as is well shown in Fig. 46. On the surface were a few large Gram-staining bacilli, but none in the deeper layers.

After two animal passages the streptococcus was injected into three rabbits and one dog. One rabbit died in twenty-four hours with streptococcemia, hemorrhage in the septum of the heart, and acute splenitis, but without lesions in the stomach. The other two died in four and eighteen days. The one dying in four days showed multiple arthritis, the other arthritis of the right knee, and a healing ulcer (5 by 3 mm.) in the cardiac end of the stomach. The dog which died in eighteen days had developed two healed ulcers of the cardiac end of the stomach, a local nephritis, fatty degeneration of the liver, and localized myocarditis.

After three animal passages the streptococcus was injected into one dog, which died from an overwhelming infection in twenty-four hours. The staphylococcus was repeatedly injected intravenously into two rabbits, neither of which developed lesions of the stomach. Mixtures of the cultures of the staphylococcus and the streptococcus fed with chopped meat and sharp particles of dried splintered bone to two dogs did not produce lesions.

CASE B.—Ulcer of the stomach in a woman twenty-eight years of age whose symptoms had existed for five years. This ulcer, which was 3 cm. from the pyloric ring, was adherent to the duodenum and the pancreas, causing hour-glass constriction.

The usual streptococcus was isolated in pure culture, and injected,

Fig. 43.—Multiple hemorrhages, necroses, and ulcerations of the mucous membrane of the stomach of Dog 42 (Case 779) four days after an intravenous injection of a streptococcus isolated from a gastric ulcer in man and passed through one animal (natural size).
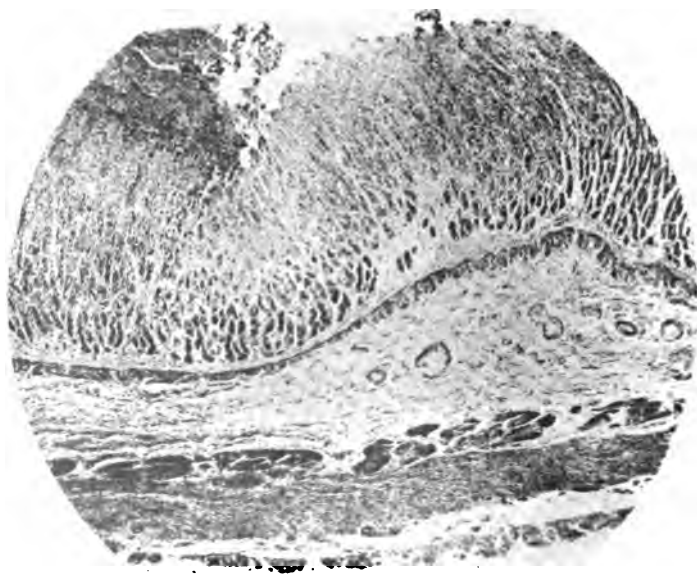
Fig. 44.— Section through the area of the stomach at *a* in Fig. 43, showing the sloughing mucous membrane, the marked hemorrhage, leukocytic infiltration, the poorly staining cells, and the aggregations of leukocytes in the dilated blood-vessels in the submucosa.   Hematoxylin and eosin (X 50).

as soon as sufficient growth could be obtained, into two rabbits and three dogs of medium size.

The rabbits died in twenty-four hours. They were examined im-
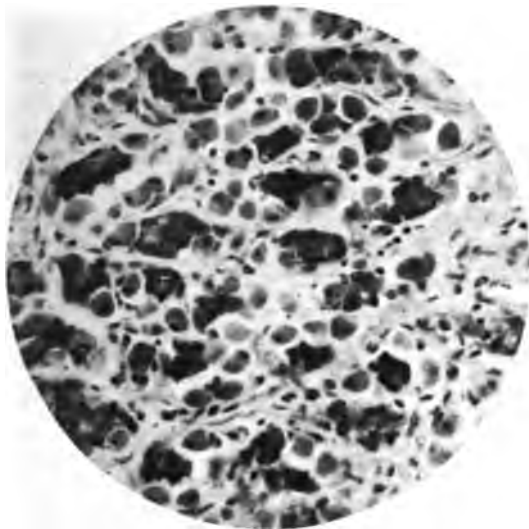
Fig. 45.—A portion of the infiltrated and necrotic mucous membrane of the ulcer shown in Fig. 44, under higher magnification. Marked disintegration and disappearance of the chief cells, leukocytic infiltration, and relatively normal appearance of the parietal cells. Hematoxylin and eosin (× 400).

Fig. 46.—Photomicrograph of a mass of diplococci and streptococci in the sloughing portion of the ulcer shown in Fig. 44. Gram-Weigert stain (× 1000).

mediately. Both disclosed marked, but localized, hemorrhages of the stomach, with gaseous distention. One showed, in addition, hemorrhages in the pericardium and in the aortic valve, while the other showed small hemorrhages in the tricuspid valve. Cultures from emulsions of the hem-

orrhagic areas in the stomach yielded many streptococci; those from the blood, a smaller number.

All three dogs had developed lesions of the stomach. The one which had received the largest dose died in twenty-four hours, showing acute dilatation of the stomach, with circumscribed hemorrhages in the cardiac end, a large amount of brownish fluid, no food, and gaseous distention. The gas in the stomach of the dog, as in both rabbits, contained large amounts of carbon dioxid. There were, in addition, hemorrhages of the mucous membrane of the colon. Another dog died in forty-eight hours, with one acute ulcer of the fundus extending through the mucous membrane, numerous small punctate hemorrhages, some of which showed beginning ulceration, and numerous small, and occasionally white, necrotic areas in the mucous membrane of the large intestine. The third dog, chloroformed eight days after injection, had developed a small round ulcer of the pylorus (5 mm. in diameter) 2.5 cm. from the pyloric ring. Cultures from the blood were sterile, while those from the ulcer gave a moderate number of non-hemolyzing streptococci.

The strain isolated from the dog which died in four hours (one animal passage) was injected into two rabbits and two cats. One rabbit died in two days, the other in thirteen days. The former showed hemorrhage in the tricuspid valve, with a beginning endocarditis, the latter what appeared as a phlegmonous gastritis, cholecystitis, medullar nephritis and pyelitis, and endocarditis. Cultures from the mucous membrane of the second rabbit yielded a large number of streptococci and a few colonies of colon bacilli. The blood was sterile.

The cat which had received the large dose showed, after twenty-four hours, marked gaseous (carbon dioxid) distention of the stomach, extensive hemorrhage of the mucous membrane of the fundus, and a moderate amount of chocolate-colored blood. Cultures from the blood gave 20 colonies; from the spleen, 40; two areas of hemorrhage in the mucous membrane yielded 2000 and 3000 colonies, and the adjacent normal mucous membrane, 40 colonies of the non-hemolyzing streptococcus.

The cat which had received the smaller dose seemed ill, ate poorly, and lost in weight for a number of weeks, then regained weight and became apparently perfectly well. It was chloroformed fourteen weeks after injection. No lesions were found except a scar (0.5 cm. in diameter) in the mucous membrane of the stomach, 2 cm. from the pyloric ring.

CASE 885.—Chronic ulcer of the stomach with perforation. An emergency operation was performed January 31, 1914, by Dr. Hirst. There were a perforating ulcer of the stomach and a beginning peritonitis. The ulcer was excised and the area inverted. The patient recovered.

Cultures yielded approximately 5000 colonies of the usual non-hemolyzing streptococcus and a few colonies of staphylococci and sarcines.

DOG 65.—Injected intravenously, February 4, with the growth from

150 c.c. of an ascites-dextrose broth of the streptococcus in its second culture.

February 14: Seemed ill, ate little, and had lost in weight.

February 22: Found dead. Stomach was distended with gas rich in carbon dioxid. It contained a small amount of brown, blood-tinged fluid, but no food. A number of small deep ulcers were found in the fundus. In two of these the inflammation extended through to the peritoneal coat, which was opaque and hyperemic. The mucous membrane of the pylorus was normal. The duodenum showed one large ulcer (1 by 2.5 cm.). The peritoneal coat here was adherent to the surrounding structures and formed the floor of the ulcer.

Sections through one of the ulcers in the stomach revealed leukocytic infiltration in the margin and in the peritoneal and subperitoneal layers, and a moderate number of diplococci. The muscular coat, however, was quite free from infiltration.

CASE 52.—Ulcer of the stomach and duodenum in a woman sixty-two years of age. The patient had had for years severe attacks of migraine. Three years previously she had had a severe attack of herpes zoster, involving the left thorax, and two years previously there had been a recurrence of severe pain in the zoster area, but no blistering. One year later she had had two severe hemorrhages from the stomach, but had made a good recovery under medical management, and was again quite free from gastric symptoms. At this time marked tartar deposit was found about the teeth, and marked gingivitis, especially at the outer aspect of the second right lower molar. The patient was advised to have her teeth put in order, but this was not done.

On August 19, 1914, she began vomiting large quantities of blood on two occasions several weeks after an attack of so-called grip. Three days after the hemorrhages from the stomach the temperature rose. Although there were no physical indications of pneumonia or other demonstrable cause, a high fever continued until death occurred.

Only a partial postmortem examination was made. The heart showed chronic mitral endocarditis. The lungs were edematous, but there was no pneumonia. The wall of the duodenum just beyond the pylorus showed two thickened, puckered areas, which produced a marked sacculation on the anterior wall, approximately 2.5 cm. in diameter. On opening the stomach there were found approximately 100 c.c. of muco-purulent material free from food. The puckered areas in the duodenum were scars of healed ulcers. Just outside of the pyloric ring, on the posterior wall, was an indurated, partially healed ulcer, 0.4 by 1 cm., having a hemorrhagic base. In the pyloric third of the stomach was an entirely healed ulcer, and one acute ulcer having a hemorrhagic base, which was not thickened. The mucous membrane of the entire stomach was hyperemic, in places edematous, and studded with numerous punctate hemorrhages, the membrane over some of the hemorrhagic

areas being eroded. The mucous membrane adjacent to the ulcer was no more hyperemic than the rest. The lymph-glands in the gastrocolic omentum were enlarged and hemorrhagic on the cut surface. No thrombosed blood-vessels in the stomach could be found. The gall-bladder was distended with a dark bile, the ducts patent. No gall-stones. The liver showed marked granular and fatty degeneration. The stomach-contents did not have an acid odor and were only slightly acid to litmus. No peritonitis.

Cultures were made from the blood, lymph-gland, liver, duodenal contents, duodenal and gastric ulcers, and from pus obtained from the depths of the inflamed gum covering the deposit of tartar on the right lower molar.

August 31: Cultures in ascites-dextrose broth from the gum gave a pure culture of a short-chained streptococcus (Fig. 42); those from the duodenal contents, the emulsion of the ulcers, the blood, the lymph-gland, and the liver, gave streptococci and colon bacilli. Ascites-dextrose-agar shake cultures from the ulcer emulsion yielded approximately 6000 colonies of streptococci and approximately 150 colonies of colon bacilli. The material withdrawn with a pipet from the margin of the duodenal ulcer—the surface having first been seared—showed mostly streptococci, but also a few colon bacilli.

Sections of the ulcer in the duodenum and of that in the stomach disclosed hemorrhage and leukocytic infiltration of the margin and base, extending through the entire thickness of the mucosa and submucosa. The muscular coat was largely replaced by connective tissue in the case of the duodenal ulcer, but not in the case of the gastric ulcer; in the latter was marked leukocytic infiltration of the peritoneal coat, but no perforation. Sections through one of the edematous and hemorrhagic areas revealed marked dilatation of the intraglandular blood-vessels, hemorrhage, and leukocytic infiltration. Gram-Weigert stains of sections of the ulcers disclosed numerous streptococci in the margins and bases of the ulcers and in the peritoneal coat. Those of the edematous areas also showed a number of streptococci. On the surface of the ulcers, as of the hemorrhagic areas, were found scattered bacilli.

The streptococcus from the tooth was injected, in the first culture, into four animals. Of these, all but one showed hemorrhage or ulcer of the stomach. The results in the case of the dog were as follows:

DOG 120.—Injected intravenously September 1, 1914, with the growth from 150 c.c. of ascites-dextrose broth of the streptococcus from the tooth.

September 3: Dog seemed well. Chloroformed. The mucous membrane of the pyloric end of the stomach was studded with numerous small, punctate hemorrhages. There were also a number of larger hemorrhages and four ulcers, from 2 to 4 mm. in diameter, near the juncture of the middle and lower thirds of the stomach. The intervening

mucous membrane was normal. The gastric contents, which had a typical odor, were highly acid in reaction. The gallbladder, appendix, pancreas, and other organs appeared normal.

September 4: Cultures from blood, bile, liver, and joint fluid were sterile. Cultures from the larger ulcer yielded 150 colonies of streptococci, those from the small ulcer, 80 colonies, while those from a hemorrhagic area without ulceration of corresponding size gave approximately 2400 colonies of the injected streptococci.

The streptococcus from the ulcer was injected, in its second culture, into twelve animals. Of these, eight developed lesions in the stomach and five lesions in the gallbladder.

After one and two animal passages, the streptococcus was injected into six more animals, giving rise to lesions in the stomach in one and to lesions in the gallbladder in three.

CASE 112.—Single woman, fifty-one years of age; bookkeeper. She had complained of pain and other symptoms in the epigastrium typical of duodenal ulcer for one year. Pain had been especially severe six weeks prior to examination. August 18, 1914, there was found by Dr. Judd a subacute ulcer of the duodenum, 1 cm. beyond the pylorus, and a chronically inflamed adherent appendix. The overlying and adjacent visceral and parietal peritoneum was very red, loosely adherent, and edematous. The location of the ulcer and the severity of the accompanying inflammation precluded excision of the ulcer. After covering the ulcer with omentum and partially occluding the pylorus, posterior gastro-enterostomy and appendectomy were done. The patient made a prompt recovery.

September 3: Cultures from the thickened and injected visceral peritoneum overlying the ulcer gave a moderate number of short-chained, non-hemolyzing streptococci and a few colonies of a Gram-staining bacillus resembling Bacillus subtilis, while the parietal peritoneum adjacent to the ulcer yielded a few colonies of the same streptococci in pure growth. The sections of the thickened visceral peritoneum showed marked fibrous thickening, perivascular round-cell and leukocytic infiltration, and hemorrhages. Diplococci were found, two of which are shown in Fig. 48.[41]

The streptococcus in its second culture was injected into four dogs, two rabbits, and one guinea-pig, all of which developed ulcer. All the dogs, one rabbit, and the guinea-pig developed duodenal ulcer; the other rabbit, ulcer of the stomach and cholecystitis. The dogs, in addition to ulcer of the duodenum, had marked hemorrhages in the stomach and the duodenum. Three of the four dogs showed a peritonitis of the lesser peritoneum surrounding the duodenal ulceration. In the dog which developed localized hemorrhages in the gallbladder the peritoneal exudate had extended to the gallbladder and to the under surface of the liver.

Fig 47.—Chronic ulcer of the duodenum in Dog 37 (Case 773) fourteen weeks after intravenous injection of a streptococcus from an excised ulcer of the duodenum in man (natural size).
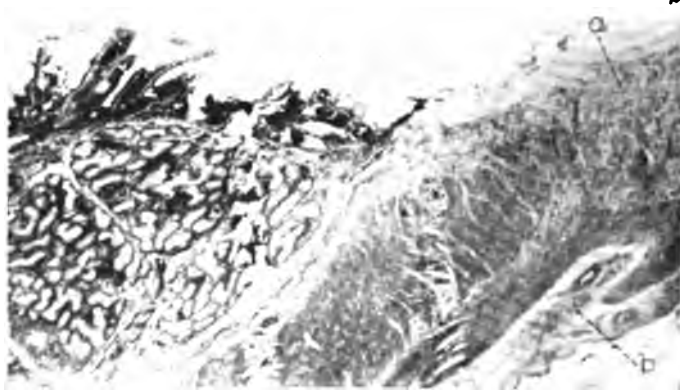
Fig. 48.—Section of the ulcer shown in Fig. 47.   Invasion of the muscular coat by connective tissue at *a* and peritoneal adhesions at *b*.   Hematoxylin and eosin (× 80).
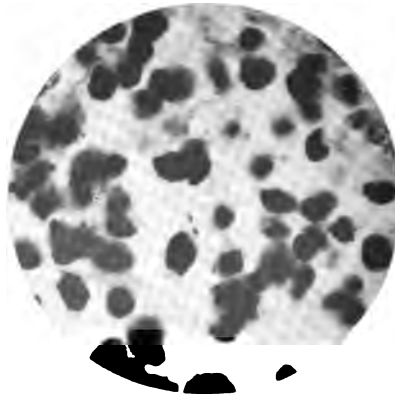
Fig. 49.—Diplococci in the margin of the ulcer shown in Fig. 48 (× 1000).

After one animal passage the strain was injected into two dogs. One developed two deep hemorrhagic ulcers in the duodenum, hemorrhages of the stomach, marked cholecystitis, localized peritonitis, and hepatitis; the other, cholecystitis and hemorrhages in the duodenum, but no ulcer. .

After two animal passages the streptococcus was injected into three dogs and two rabbits. One dog developed an ulcer in the pyloric end of the stomach, endocarditis, and infarcts of the kidney; one, cholecystitis and focal nephritis; the third, ulcer of the stomach and duodenum. One rabbit had ulcer of the stomach, and the other ulcer of the duodenum.

DOG 134.—Injected intravenously, November 4, 1914, seventy-eight days after the original cultures had been made, with the growth from 60 c.c. of an ascites-dextrose broth of the streptococcus from the ulcer in Case 112.

November 5: Found dead. The mucous membrane of the stomach was hyperemic, with numerous small hemorrhages, especially in areas in the pyloric end. The first portion of the duodenum, which was markedly hyperemic, contained three hemorrhagic areas from 5 to 6 cm. in diameter. The mucous membrane in the center of one of these areas just outside the pyloric ring was necrotic and ulcerated. The rest of the mucous membrane of the duodenum and intestine was normal, except for small hemorrhages, especially in the lymph-follicles. The peritoneum of the upper portion of the small intestine was hyperemic and opaque, while over the duodenum, gallbladder, and the under surface of the liver there was a thin layer of loosely adherent fibrinous exudate. The mucous membrane of the gallbladder was normal. There was a pea-sized, hemorrhagic lymph-gland adjacent to the duodenum. The mesenteric glands were normal. No other gross lesions.

November 7: Cultures from the crushed area of hemorrhage in the duodenum yielded fully 10,000 colonies of streptococci and only 12 colonies of colon bacilli, and the blood a moderate number of gray-producing, non-hemolyzing colonies of streptococci. The bile and peritoneal exudate revealed a large number of pure streptococci. The joint fluid was sterile.

DOG 142.—Injected intravenously September 11, 1914, with the growth from 75 c.c. of an ascites-dextrose-broth culture of Strain 112 after one animal passage.

September 12: Dead. There was marked hemorrhage of the cardiac end of the stomach, of the duodenum, and of the small intestines. The gallbladder was markedly hemorrhagic and edematous, especially over the fundus, where the wall measured from 0.4 to 0.6 cm. The edema was most marked in the submucosa. Mucous membrane swollen, but not ulcerated. Fluid expressed from the wall of the gallbladder and the surrounding structures bile-stained. Walls of the cystic and common

ducts also edematous. Lymph-glands adjacent to the common duct, hemorrhagic. Except for subendocardial hemorrhages, particularly of the left ventricle, no other noteworthy lesions were found. Smears from the edematous fluid from the wall of the gallbladder gave a moderate number of streptococci.

September 13: Blood-agar plate cultures of the blood yielded 50, of the bile 2500, and of the wall of the gallbladder 8000, colonies of non-hemolyzing streptococci. The bile showed, in addition, 5 colonies of colon bacilli. Cultures from the bile in tall columns of ascites-dextrose agar gave streptococci, gas bacilli, and colon bacilli; those from the wall of the gallbladder, streptococci and gas bacilli; and those from the liver, a few colonies of streptococci.

DoG 156.—Injected September 19, 24, and October 2, with the growth from 20, 30, and 40 c.c., respectively, of an ascites-dextrose tissue broth of Strain 112, after two animal passages.

October 10: Seemed ill and very weak. Chloroformed, and examined at once. Mucous membrane and tissues everywhere pale, the blood showing only 50 per cent. hemoglobin. The stomach, free from food, contained a small amount of brownish material resembling altered blood. The mucous membrane of the stomach contained approximately 10 small erosions surrounded by whitish, necrotic, swollen areas, and a number of small ulcers filled with adherent brownish blood-clots. There was one large deep ulcer, 0.6 by 1 cm., in the duodenum just above the ampulla of Vater (Fig. 50). The margin was edematous and necrotic and the base was filled with clotted blood. The liver showed marked fatty degeneration. The lumen of the small and large intestines contained a moderate amount of partially digested blood. No other noteworthy lesions. Smears from the necrotic margin of the ulcer in the duodenum revealed many leukocytes, Gram-staining diplococci, and short chains.

October 15: Cultures from the blood yielded non-hemolyzing streptococci, and those from the bile, gas bacilli. Sections through the base of the ulcer showed in the center complete absence of mucous membrane and submucosa, and necrosis of one-third of the circular layer of the muscular coat. There was leukocytic infiltration between the disintegrating epithelial cells in the submucosa, chiefly around vessels, along the connective-tissue stroma, between muscle-bundles, and beneath and in the thickened and adherent peritoneal coat. There was no extravasation of red blood-corpuscles. The portion of the base of the ulcer which had not yet entirely sloughed was composed of poorly staining connective-tissue stroma, in which were fragmented cells, leukocytes, thrombosed vessels running at right angles to the floor of the ulcer, and two large, thrombosed vessels in the submucosa (Fig. 51). The thrombi, which were partially organized, contained a moderate number of leukocytes. In several sections of a large series studied there was marked leukocytic infiltration surrounding the thrombosed vessel in the submucosa. Gram-

Weigert stains showed a moderate number of diplococci, chiefly in the area of leukocytic infiltration, and a few in one of the thrombi in the small

Fig. 50.—Ulcer of duodenum at *a* in Dog 156 (Case 112), eighteen days after intravenous injection of a strepto coccus from the peritoneal coat of an ulcer in the duodenum in man (Case 112) (natural size).
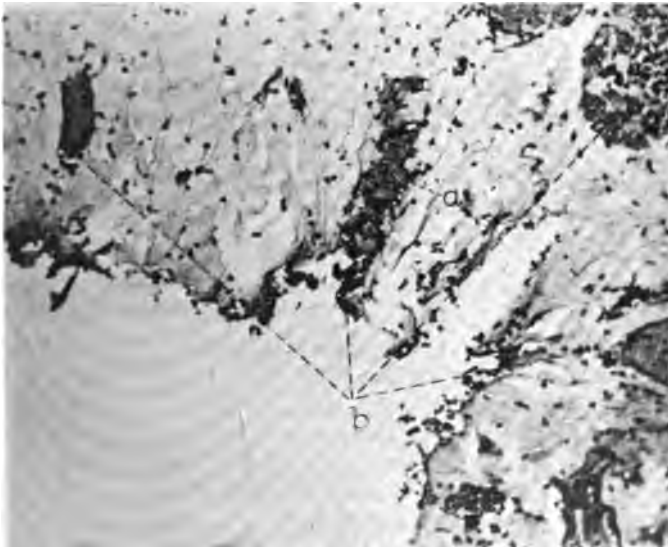
Fig. 51.—Section of the ulcer in the duodenum shown in Fig. 50. Ragged base, poorly staining connective-tissue stroma, moderate leukocytic infiltration, thrombosed vessels (*b*), and a large number of leukocytes in the thrombi. Hematoxylin and eosin (× 120).

vessels shown in Fig. 52. On the surface of the ulcerated area and the adjacent normal mucous membrane were found a few scattered cocci and large bacilli.

CASE 236.—Recurring ulcer of the stomach in a young man.* The patient had developed typical symptoms of ulcer of the stomach six months before, after ulceration of a tooth. He had completely recovered under medical management. Since that time he had had a discharging sinus, as a result of trouble with the tooth, which alternately healed, formed a blister, and then again discharged pus. There had been a sudden recurrence of the ulcer of the stomach associated with hemorrhage five weeks prior to examination.

On January 22, 1915, two days previous to the extraction of the tooth, a culture was made from. pus withdrawn from the sinus after sterilization of the surface and insertion of a pipet for a depth of 1 cm. A blood-agar plate culture gave an almost pure culture of Streptococcus viridans, with a few colonies of hemolytic streptococci. Ascites-dextrose broth cultures

Fig. 52.—Photomicrograph of two diplococci found in the thrombosed vessel at *a* in the ulcer shown in Fig. 51. Gram-Weigert stain (× 1000).

yielded a pure growth of a short-chained streptococcus. The cultures from the tooth-pulp, two days later, yielded exactly similar results.

Injection of this strain into guinea-pigs, rabbits, and dogs showed a most pronounced tendency on the part of the organism to lodge in the mucous membrane of the stomach, producing hemorrhages and ulceration. Intravenous injection of the strain from the sinus was made into two rabbits and one dog. The dog developed ulcer in the duodenum; one rabbit had hemorrhage and ulcer of the cardiac end of the stomach, and the other rabbit arthritis, but no lesions of the stomach.

The cultures from one of the ulcers in the dog gave the streptococcus in pure growth in broth and in ascites-dextrose agar (17 colonies). The broth culture, injected intravenously into one rabbit and one guinea-pig, produced hemorrhage or ulcer in both; injected intraperitoneally into one rabbit and one guinea-pig, it produced in the rabbit an acute ulcer (2 by 3 cm.) in the lesser curvature of the stomach, but no lesions in the

* I am indebted to Dr. Sippy for this case.

guinea-pig; injected intrapleurally into one guinea-pig, it caused two small ulcers in the pyloric end of the stomach; injected subcutaneously into one guinea-pig, it caused no lesions in the stomach. The streptococcus culture from the tooth was injected intravenously into one

Fig. 53.—Streptococci in the peritoneal coat of a perforating ulcer of the stomach of Rabbit 652 thirty-five days after intravenous injection of the streptococcus isolated from a lymph-gland draining a perforating ulcer of the duodenum in man (Case 947). Gram-Weigert stain (× 1200).

Fig. 54.—Marked ulceration of the stomach of Guinea-pig 12 twenty-four hours after intravenous injection of a streptococcus from a suppurating frontal sinus in a man with ulcer of the stomach (Case 213).

Fig. 55.—Chains of diplococci in the margin of the ulcerated mucous membrane shown in Fig. 54. Gram-Weigert stain (× 1000).

Fig. 56.—Hemorrhage in the duodenum of Rabbit 792 forty-eight hours after intravenous injection of a streptococcus from the tonsil in a patient with arthritis deformans and probable ulcer of the stomach (Case 163) (natural size).
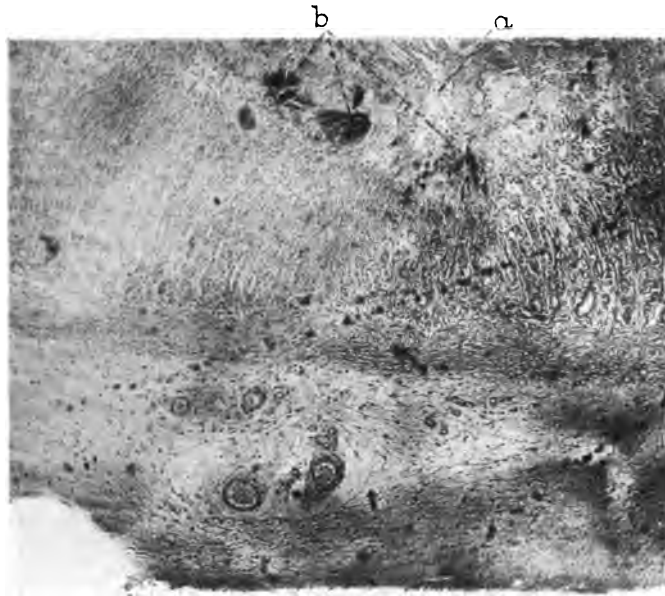
Fig. 57.—Ulcer of the mucous membrane of the stomach of Rabbit 787 three days after intravenous injection of an emulsion of the tonsils from a case of arthritis deformans with symptoms suggesting ulcer of the stomach (Case 163). Note the dark radiating areas at *b* and the apex of the ulcerated area shown at *a*. Hematoxylin and eosin (× 60).
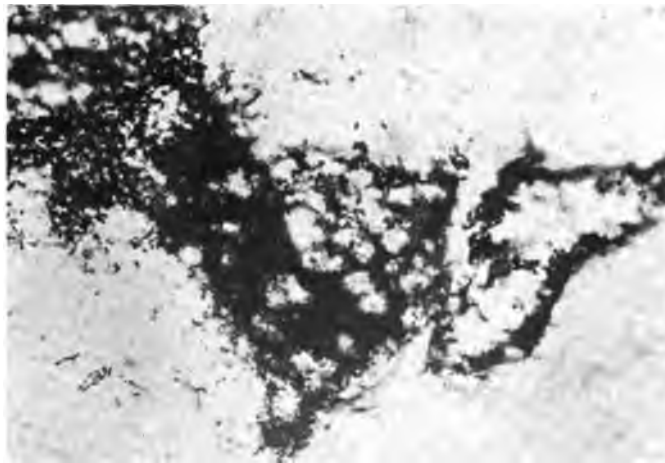
Fig. 58.—A higher magnification of the dark radiating area at *b* in Fig. 57, showing an enormous number of streptococci (× 1200).
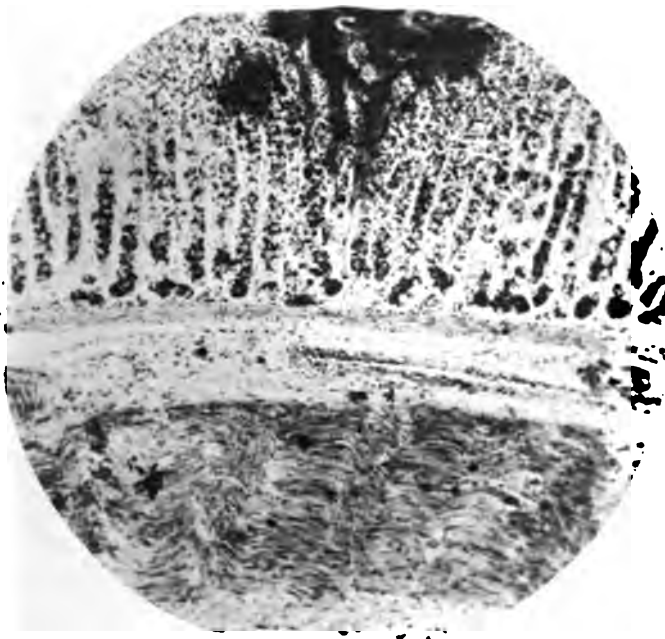
Fig. 59.—Section of the wall of the stomach of Rabbit 68 showing wedge-shaped area of leukocytic infiltration, hemorrhage, and beginning ulceration, forty-eight hours after intravenous injection of a streptococcus isolated from the tonsil in herpes zoster and passed through one animal. Hematoxylin and eosin (Case 281) (X 80).
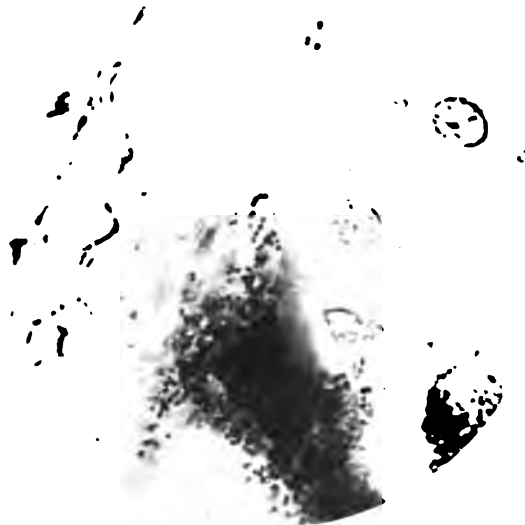
Fig. 60.—Streptococci at the apex of the wedge-shaped area shown in Fig. 59. Gram-Weigert (X 1200).

rabbit and one dog, and intraperitoneally into one guinea-pig. All developed hemorrhage and ulcer of the stomach or of the duodenum. Cultures from one ulcer from each of seven animals yielded from 5 to 40 colonies of streptococci, irrespectively of whether the injection had been made intravenously, intraperitoneally, or intrapleurally.

CASE 227.—An ulcer of the stomach in a physician of middle age. There was a history of severe recurring attacks of tonsillitis and rhinitis for years. On April 21, 1914, during an attack of acute rhinitis and acute indigestion resembling ulcer there was isolated a pure culture of a green-producing streptococcus from the mucopurulent discharge from the nose. This was injected into five animals. Of these, two developed ulcer of
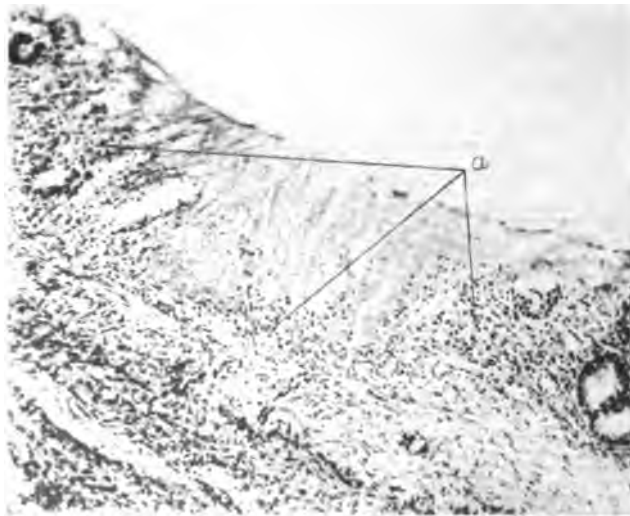
Fig. 61.—Section of an ulcer of the stomach of Dog 22 twelve days after intravenous injection of a streptococcus from rheumatism. Note its wedge shape and the round-cell infiltration at *a* between the necrotic and more normal tissue. Hematoxylin and eosin (× 60).

the stomach, one hemorrhages of the stomach, and two cholecystitis. No particular importance was attached to these findings at that time.

December 19: The symptoms of gastric ulcer were typical. The tonsils showing marked infection, tonsillectomy was done. Salt-solution suspensions of the extirpated and washed tonsils caused hemorrhage or ulcer of the stomach in two rabbits. Cultures from the tonsils injected into six animals produced hemorrhages or ulcer of the stomach in four.

After the removal of the tonsils, while the patient was being treated with an autogenous vaccine prepared from the streptococcus isolated from the ulcer in one of the animals, the symptoms of ulcer were reduced for a short time, but they returned and persisted in spite of strict medical management (Dr. Frick).

February 27: The teeth showed the presence of a number of pyorrheal pockets. Cultures from the pus from these pockets injected into one dog produced hemorrhage and ulcer of the stomach. On the basis of these findings the involved teeth were extracted on August 15, 1915, the symptoms of ulcer having persisted during the interval. The patient was then placed on strict medical treatment for ulcer, and has since been free from symptoms and has regained his former weight.

CASE 531.—Recurring ulcer of the stomach in a woman thirty-four years of age (Dr. Plummer). The trouble had begun eight years before, with recurring attacks of sharp, cramp-like pain in the epigastrium. The attacks were usually associated with nausea, in former years with vomiting and numerous hemorrhages from the stomach, and were followed by soreness in the epigastrium. These attacks, which always followed tonsillitis, lasted from ten to fourteen days and were followed by intervals of three or four months of almost complete relief. Systolic blood-pressure, 122; temperature, 99.2° F.; hemoglobin, 70 per cent.; urine normal, except for a small amount of albumin. A test-meal showed a total acidity of 48; free hydrochloric acid, 28; combined acids, 20, and no occult blood. An x-ray of the chest and stomach was negative. Tonsils small and only moderately infected. Slight tenderness over the right abdomen, most marked over the right lower quadrant, but no muscle spasm. On account of the apparent etiologic relation between the tonsils and the attacks, tonsillectomy was advised. The extirpated tonsils, which were small, revealed only a moderate grade of infection.

Cultures gave chiefly Streptococcus viridans, a few hemolytic streptococci, and staphylococci. The broth cultures for injection yielded chiefly rather long chained streptococci.

These cultures were injected intravenously into two guinea-pigs and four rabbits. All but one rabbit and one guinea-pig showed either hemorrhage or ulcer, or both, of the stomach or of the duodenum. The rabbit injected with 3 c.c. of the emulsion from the tonsils developed both hemorrhage and ulcer of the stomach. Only two of the animals died. The rest seemed well. An ulcer which was cultured yielded 50 colonies of streptococci in pure growth. Since the tonsillectomy, the patient has gone for a longer interval without gastric attack than at any time during a period of eight years.

In previous papers[40, 43] I have pointed out that when strains of streptococci of low virulence are passed successively through animals, their place of localization changes with returning virulence, and that when these strains reach the stage at which they give rise to muscle lesions, they are apt also to produce ulcer of the stomach and focal nephritis. The following experiment will serve to illustrate these observations:

DOG 25.—Injected intravenously March 20, 1913, with the growth

from 240 c.c. of an ascites-dextrose broth culture of streptococcus (R51A[30]) isolated eleven years previously as a pneumococcus in pneumonia. It had lost practically all virulence years before, had acquired hemolytic properties, and was now in the twentieth animal passage.

March 27: The dog was lame in the left front leg.

March 28: Turbid fluid from both knee-joints.

March 29: Right wrist was swollen and tender; the animal limped and was sensitive over muscles; movements caused pain.

April 8: Found dead, body warm. Marked pallor of all tissues;
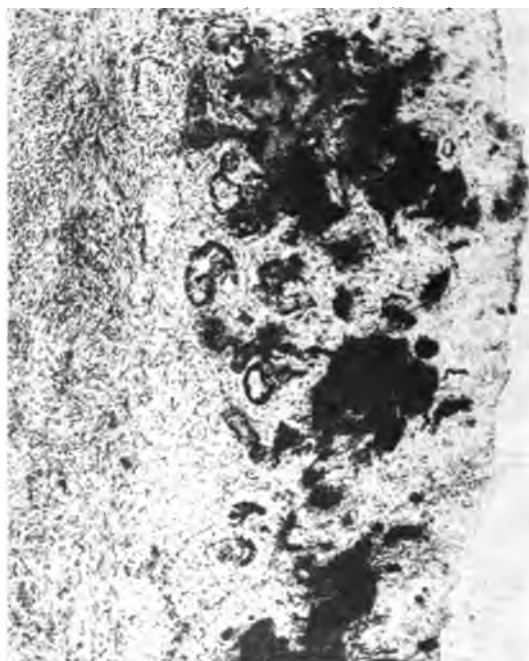
Fig. 62.—Section through the base of a large ulcer in the duodenum in Dog 25 (Case 531) nineteen days after intravenous injection of a streptococcus isolated eleven years previously as a pneumococcus. Marked hemorrhage, leukocytic infiltration, and connective-tissue formation. Neutral gentian ($\times$ 60).

hemoglobin, 40 per cent. Moderate amount of altered blood in stomach. There was one large ulcer (1 by 3 cm.) in the duodenum and one smaller ulcer (0.5 by 1 cm.) in the pyloric ring, while the rest of the stomach showed areas of hemorrhage and small ulcers. The margins of the ulcers, which were infiltrated, appeared necrotic. The ulceration in the duodenum had extended to the peritoneal coat, where there were peritoneal adhesions. The muscles contained numerous whitish streaks, especially the superficial muscles of the neck, shoulders, thorax, and diaphragm. The myocardium, which was flabby, contained a moderate number of whitish areas. Similar lesions were found in the non-striated muscle-

fibers of the large and small intestines. The kidneys showed the picture of focal and ascending nephritis. There was present also suppurative conjunctivitis of the right eye, associated with hemorrhages of the sclera at the limbus.

Sections of the ulcer of the pyloric end of the stomach showed marked leukocytic infiltration and hemorrhage in its base, degeneration of the mucous glands, and beginning fibrosis (Fig. 62). Stains for bacteria showed a moderate number of diplococci in the submucosa and in the ulcerated area.

RESULTS

The details of these experiments suffice to illustrate the results obtained.

The injection of staphylococci and of Bacillus subtilis from four, and of the yeasts from one, of the ulcers isolated in the earlier cases, produced no lesions in the stomach, and hence were considered accidental invaders.

Cultures of streptococci which in the earlier experiments had proved able to produce ulcer when injected intravenously, failed to do so when injected into dogs fed with mixtures of meat and sharp particles of bone.

In the table is given a summary of all the results following intravenous injection of streptococci from ulcer. Hemorrhage and ulcer of the mucous membrane of the stomach or of the duodenum occurred following injection of 19 strains when first isolated in 61 per cent. and 60 per cent. respectively of 117 animals injected. This is in marked contrast to an incidence of 20 per cent. hemorrhages and 8 per cent. ulcers following injection of 180 strains of streptococci from sources other than ulcer.

It should be emphasized here that these results were not obtained during a short interval only, but that the experiments extended over a period of three years, were done in different localities, and at all seasons of the year. They included altogether six species of animals (dog, rabbit, guinea-pig, monkey, cat, and mouse).

The selective affinity for the stomach and the duodenum disappeared both after cultivation of the bacteria on artificial media for from one to six weeks and after animal passage, the incidence of ulcer dropping from 60 per cent. to 0 per cent. after cultivation and to 33 per cent. after animal passage. The strains kept on artificial media acquired greater affinity for the appendix. The strains passed through animals acquired greater affinity for the gallbladder and the pancreas.[41] While the affinity for the stomach was usually more marked in the streptococci from the ulcer itself than in those from the focus of infection, the latter had an unmistakable affinity also. In the case of recurring ulcer of the

ELECTIVE LOCALIZATION OF STREPTOCOCCI FROM ULCER OF THE STOMACH

The Time of the Injection of Streptococci	Strains	Animals Injected	Appendix	Stomach and Duodenum		Gall-blad-der	Pan-creas	Intes-tines	Joints	Endo-car-dium	Peri-car-dium	Myo-car-dium	Muscles	Kidney	Lung
				Hemorrhage	Ulcer										
When isolated	23	117	2	61	60	20	3	7	16	12	4	5	0	5	0
Later	8	22	5	5	0	5	0	0	18	14	0	0	0	0	0
After animal passage	7	39	0	23	33	30	15	15	21	5	0	3	3	8	15

PERCENTAGE OF ANIMALS SHOWING LESIONS IN:

stomach (Case 236) following an ulcerated tooth the streptococcus from the pus from the sinus showed an affinity for the stomach so marked that it produced ulcer not only after intravenous, but also after intraperitoneal and intrapleural, injections.

In the case of recurring ulcer (Case 531) in which the attacks always followed tonsillitis, ulcer of the stomach followed injection of the bacteria directly from the extirpated tonsils and of the primary cultures from the tonsils, in all but two of seven animals injected. Streptococci from the alveolar abscess at the apex of an extracted tooth in a patient with acute ulcer of the stomach and gastric hemorrhage produced, on intravenous injection, hemorrhage and ulceration of the stomach or of the duodenum in two dogs and in one of two rabbits injected. In another case of acute ulcer following an attack of grip, cultures from the tonsil and from the infected area about the left lower wisdom tooth produced a hemorrhagic ulcer in the lesser curvature 2 cm. from the pyloric ring in two rabbits, both of which seemed well at the time they were chloroformed, seventy-two hours after injection.

In some instances the strains from duodenal ulcers showed an unmistakable tendency to produce ulcer in the duodenum oftener than in the stomach (Cases 773 and 112). Not only did the strain from the peritoneal coat of the ulcer in Case 112 show this to a striking degree, but in a number of animals the infection perforated the wall of the duodenum and produced a localized peritonitis like that present in the patient. Some of the strains from gastric ulcer tended to produce ulcer in the stomach oftener than in the duodenum (Case 779). This selective localization occurred too often to be accidental. In other instances

no such definite relationship between the place of isolation and the place of localization was shown.

Either or both hemorrhage and ulcer of the stomach or of the duodenum followed injection of all the strains from ulcer in a total of 93 animals (83 per cent.). Hemorrhage occurred in the pyloric portion in 38 instances, in the fundus in 34, and in the duodenum in 20; ulcer occurred in the pyloric portion in 28, in the fundus in 32, and in the duodenum in 14. Either or both hemorrhage and ulcer followed injection of strains of streptococci from sources other than ulcer in a total of 99 animals (26 per cent.). In these, hemorrhage occurred in the pyloric portion in 38 instances, in the fundus in 29, and in the duodenum in 27; ulcer occurred in the pyloric portion in 24, in the fundus in 14, and in the duodenum in 7. The location of the ulcer corresponds to the location of the hemorrhage and the location of both lesions following injection of streptococci from ulcer and other sources is comparatively fixed, being most often in the pyloric portion, along the lesser curvature, or in the duodenum, and least often in the fundus of the stomach.

In summarizing the locations of 25 ulcers, which were disclosed from one to seventeen weeks after the primary injection, many of which, chiefly in dogs, had taken on features typical of chronic ulcer, it was found that 12 were in the pyloric portion, 4 being along the lesser curvature, 2 in the fundus, and 7 in the duodenum. Healing ulcer, or scars of healed ulcers, were found in 7 instances, from eighteen to one hundred and twenty days after injections. All but 2 of these were situated in the fundus, the others in the pyloric portion.

The location of the experimental ulcers, therefore, corresponds strikingly to the location of ulcer in man, as found at autopsy and in the operating room (Mayo[44]). The duodenal ulcers occurred usually just outside (Fig. 56), and always within 2 inches of, the pyloric ring. In the dogs they were found chiefly in the anterior and posterior walls. Hemorrhage and ulceration at the ampulla occurred oftener in the rabbits than in the dogs. In one such ulcer the orifice was plugged with mucopus and the common duct was edematous.

Severe or fatal hemorrhage occurred from the more chronic ulcers in 7 instances. Three of the ulcers were situated in the pyloric portion of the stomach and 4 in the duodenum. Four of these showed thrombosis of blood-vessels in the submucosa.

In some cases the anemia was out of all proportion to the amount of blood found in the stomach and bowel at autopsy. This indicated

that repeated hemorrhages had occurred, or that a slight oozing had persisted for a long time.

The incidence of ulcer following injection of the streptococci from cholecystitis (15 per cent.), acute appendicitis (1 per cent.), rheumatic fever (18 per cent.), herpes zoster (8 per cent.), and other sources, corresponds in a general way to the incidence of ulcer in those diseases in man.

The chief difference between the lesions in the stomach or the duodenum following injection of the strains from ulcer and those following injection of strains from other sources, was one of total incidence and degree rather than of kind, the strains from ulcer showing by far the greater affinity for the stomach and duodenum. The lesions in both cases were due to localized infection of the mucous membrane, usually demonstrable at the time of examination.

The results given in the table were obtained without special attention to the time of injection of the bacteria in relation to the functional activity of the stomach. The fact that in a given series of animals injected with the same strain there were one or two in which the stomach showed no lesions whatever when the stomachs of all the rest showed marked lesions, indicates that the state of function is of importance in determining the localization and production of ulcer.

Colon bacilli were almost always absent in both duodenal and gastric ulcer in animals which were chloroformed. This is in accord with the fact that colon bacilli were absent in nearly all the ulcers in man excised at operation.[41]

DESCRIPTION OF THE ULCERS

In most instances there occurs a primary lodgment and growth of bacteria in the interstitial tissue of the glands and between the cells, followed by hemorrhage, necrosis, and ulceration. The loss of tissue usually begins in the center of the hemorrhagic infiltrated and necrotic area as early as eighteen hours after injection, and spreads to the periphery. The surrounding blood-vessels are congested. In some instances the ulcer forms without a preceding hemorrhage, in circumscribed grayish, swollen, necrotic areas. The ulcers are deeper in the center and penetrate rapidly to the muscularis mucosæ. The base in the acute ulcer is hemorrhagic, while in the more chronic type it is clean.

Microscopically, both the circumscribed hemorrhage and the ulcer are cone-shaped, with the base of the cone at the surface and the apex at the muscularis mucosæ. The streptococci lodge in the fine capillary

network about the gland tubules or tissue spaces, and multiply so that in twenty-four or forty-eight hours there are often enormous numbers of streptococci at the apex of a hemorrhagic area (Figs. 55, 58, and 60). A necrotic process surrounds this area, and as the overlying mucous membrane sloughs it carries with it most of the bacteria (Fig. 46).

This finding explains the observations made repeatedly; namely, that the cultures from the ulcerated area often show fewer colonies than those from adjoining areas of hemorrhage (experiment on Dog 120 with streptococcus from the tooth in Case 52). The number of colonies, especially if the animal has been dead for a time, is often surprisingly
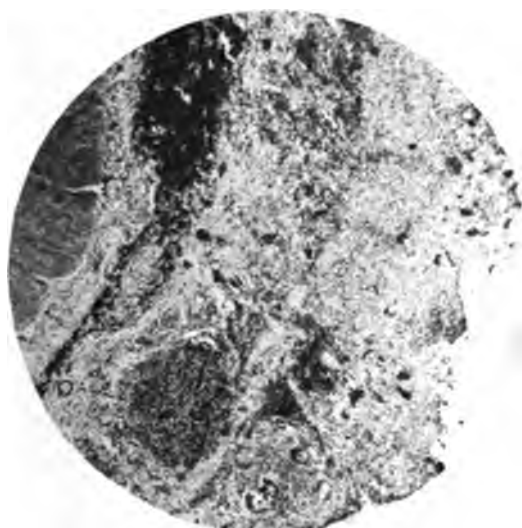
Fig. 63.—"Follicular" ulcer of the pylorus of a dog following repeated injections of a streptococcus from a lymph-gland at the pole of the thyroid in exophthalmic goiter.   There is marked hemorrhage in the submucosa and surrounding the lymph-follicle, infiltration, necrosis, connective-tissue formation; the muscular layer is normal. Neutral gentian ($\times$ 40).

small, ranging usually from relatively few to thousands. From a careful study of numerous sections and of the results of the cultures it is certain that following the primary sloughing the number of streptococci in the remaining more or less healthy tissue is not usually very large, bacteria being often hard to find.

The cellular infiltration surrounding the chronic ulcers is usually not marked, but frequently extends into the submucosa, the muscular layer, and at times through the peritoneal coat. The connective-tissue formation is well advanced in some ulcers and at times extends far beyond the ulcerated area (Fig. 62). In some instances it involves the muscular

layer and peritoneal coat (Fig. 48). In the chronic ulcers, both in man and in animals, the streptococci present are few in number and are found chiefly in the areas showing cellular infiltration surrounding the necrotic process, along the supporting tissue, the gland tubules, along partition membranes, and not infrequently in the subperitoneum. There are often marked intraglandular infiltration, disintegration, and disappearance of the chief cells of the gastric tubules, while the parietal cells remain unaffected (Fig. 45). This is in agreement with the findings of von Korczynski and Jaworski[45] in the case of ulcer in man. Completely or partially thrombosed blood-vessels have been found in or adjoining the experimentally produced ulcers in 9 instances. In 3 of these the thrombi contained streptococci (Dog 156, Case 112, and Figs. 51 and 52).

In 4 instances only the ulcer appeared to be secondary to a primary infection in the lymph-follicles, but in none of these was the evidence entirely convincing (Fig. 63).

THE MECHANISM OF THE FORMATION OF THE ULCER

Bensley and Harvey[46] have shown that the hydrochloric acid in the normal stomach is formed on the free surface. It occurred to me that possibly the localized infection might alter the secretory activity of the cells, and that the hydrochloric acid might be formed within the cells in the depths of the mucous membrane, which would then directly become digested and the ulcer result. An attempt was therefore made to study this point by the use of indicators under the conditions given by Bensley and Harvey.*

The difficulties to be overcome were obviously great. The affinity of many strains for the stomach is transient. The size of the injection had to be regulated so that the amount of ulceration and general illness would not be sufficient to interfere with the appetite of the animal. The lesion had to be in the acid-secreting portion. The process had to be studied after distinct lesions had taken place, but preferably before marked ulceration had occurred. Repeated experiments resulted in failures, but in two rabbits and one dog all necessary requirements were fulfilled. Only one experiment will be cited here.

RABBIT 676.—Injected intravenously June 28, 1914, with the growth from 45 c.c. of an ascites-dextrose tissue broth of a streptococcus (31) from ulcer in man.

* I wish here to express my appreciation to Dr. Harvey for valuable aid and suggestions in the use of their technic.

June 29: Seemed well; was fed cabbage and grass; ate heartily; killed by sudden blow on the head. Stomach removed and opened at once. The content was highly acid to litmus. The mucous membrane was washed for an instant in cold water. There was a hemorrhage with beginning ulceration in the mucous membrane of the cardiac end of the stomach (3 by 2 mm.). One-half of the ulcer was saved for cultures, the other studied at once. Bits of the hemorrhagic mucous membrane with beginning ulceration in the center and adjoining normal mucous membrane were placed in a saturated solution of cyanamin bichlorid, in salt solution, and in a solution of one part of neutral red to 10,000 parts of salt solution, where they were allowed to remain for a few minutes. They were then rapidly mounted on slides in the solutions, pressed flat with a cover-glass, and examined.

The normal mucous membrane presented the picture described by Bensley and Harvey. There was no acid in the glands, but an abundance in the foveola (blue in cyanamin solution, red in neutral-red solution). There was no acid in the foveola in the hemorrhagic area, or in that immediately surrounding this area. The gland-cells in the hemorrhagic area became acid more rapidly than the adjacent more normal cells. There was no evidence of secretion in the parietal cells.

June 30: Cultures from blood, bile, liver, and joint fluid were negative, while those from the ulcer showed 50 colonies of streptococci.

The results of this study indicate that the infection inhibits locally the secretory function of the gastric cells, and that the digestion of the damaged cells is due to the gastric juice formed in other portions of the stomach. The infection in the fundus is not essentially different from infection in the duodenum or in the pylorus or in the other tissues.

THE STREPTOCOCCI

The streptococci isolated from the ulcers produced small, moist, non-adherent, discrete, grayish-brown or grayish-green colonies on blood (human) agar plates, and produced short chains and masses of coccus-like forms (Fig. 41), a diffuse turbidity with a flocculent sediment, and much acid in dextrose broth and ascites-dextrose broth. They acidify, but usually do not coagulate, milk. They are free from capsule, are bile-insoluble, and freely susceptible to phagocytosis. They do not ferment inulin but produce much acid and precipitate ascites-dextrose agar. They resembled very closely those isolated in appendicitis and chole-cystitis. In only one instance were typical hemolytic streptococci isolated from the ulcer wall, and in no instance were they isolated from the lymph-glands draining the ulcer.

In the primary cultures smears from single colonies, especially from

those in ascites-dextrose agar, showed at times so little chain-formation and so many clumps made up of small cocci and indistinct diplococci that it was difficult to decide whether a given colony represented a mixture of streptococci and staphylococci or a peculiar streptococcus. Subcultures on blood-agar plates or in broth usually cleared up the point.

The cultures from the supposed atrium of infection showed chiefly non-hemolyzing streptococci. In most instances, however, hemolyzing streptococci in small numbers, together with a few colonies of staphylococci, were also present, and the usual number of Gram-negative cocci resembling Micrococcus catarrhalis. Injection of mixtures of hemolyzing and non-hemolyzing streptococci was usually followed by ulcer and arthritis. The former, in some instances, proved to be due to Streptococcus viridans, the latter to hemolytic streptococci. In no instance did the hemolyzing streptococcus show predilection for the stomach.

Streptococci from the most chronic ulcers produced the smallest colonies, the least amount of green on blood-agar plates, and the shortest chains in ascites-dextrose broth and other liquid media. Most of the strains resembled Streptococcus fæcalis (Horder). A number produced a narrow zone of hemolysis peripheral to the primary green zone. Blood-corpuscles in broth cultures were usually not dissolved, or were dissolved very slowly. The strains from the two acute ulcers, as did most of the strains from the supposed atrium of infection (Fig. 42) which had affinity for the stomach, produced a larger amount of green on blood-agar. In all the strains tested, animal passage tended to increase the size of the colonies and the amount of green-production. Two of the strains (from Cases 773 and 779) appeared to take on hemolytic properties in dogs during, respectively, the fifth and sixth animal passages. The changes which these streptococci underwent are in accord with those observed by me in a special study of this question several years ago.[43]

The property on which the characteristic localization depended could be preserved best in the depth of the original cultures in ascites-dextrose broth and in salt solution, containing pieces of tissue, kept in the ice-chest. Cultural and other changes were often not demonstrable, as the strains lost their power to produce ulcer as a result of cultivation on artificial media.

The virulence on isolation was relatively low, as shown by the fact that intraperitoneal injection into mice of large doses of seven strains isolated from chronic ulcer was followed by recovery in all; as shown also by the fact that 57 per cent. of the animals injected were chloro-

formed after they had seemingly recovered from the effects of even large doses of the culture, and that the blood in 55 per cent. was sterile at necropsy, notwithstanding the fact that many animals were examined in from twenty-four to forty-eight hours after injection. This is in sharp contrast to the results in the animals showing ulcer following injection of streptococci from sources other than ulcer. Here 91 per cent. died from the effects of the injection, and 80 per cent. showed streptococci in the blood. The limited power of the strains from ulcer to invade the blood or other structures is shown further by the fact that the cultures from the joint fluid yielded streptococci in only 22 per cent. of 40 tested, while the joint fluid in animals showing ulcer after injection with streptococci from sources other than ulcer showed streptococci in 80 per cent. of 39 tested. The injected streptococcus was found in the bile, often in large numbers, in approximately 50 per cent. of both sets of animals, irrespectively of whether or not there were lesions in the gallbladder or bile-ducts. The size and moistness of the colonies and the amount of green-production on blood-agar became greater as the virulence was increased after successive animal passages. In a number of these strains there appeared a distinct but narrow capsule. The strains from ulcer resembled in virulence and in other features those isolated by Dudgeon and Sargent[38] from the edges of perforating ulcer.

The details of the fermentative powers are reserved for a separate paper. It should be stated, however, that the fermentative powers of 12 strains in the various sugars were tested repeatedly. The fermentative powers of the various strains were not identical and fluctuated considerably. Acid was produced in dextrose by all. Lactose was fermented in all but 6 instances. Saccharose was fermented in 14 of 20 tests. Acid was produced in raffinose in only 8 of 52 instances, in mannite in 34 of 60 tests, in salicin in 46 of 55 tests, and in inulin in only 3 of 64. The three strains which fermented inulin produced green colonies on blood-agar, and resembled pneumococci morphologically.

Although the different strains from the ulcers and foci of infection are much alike, their fermentative and other features differ in certain important respects. They are not sufficiently alike to warrant considering them a distinct or specific species.

General Discussion

The fact that the dogs fed with mixtures of meat, sharp particles of bone, and streptococci, failed to develop ulcer, and the fact that cer-

tain persons have swallowed splinters of glass many times without developing ulcer, indicate that local injury from swallowed food, or even local invasion of bacteria from the mucous membrane, is rarely, if ever, the cause of ulcer.

In the light of these experiments the thrombosis in ulcer in man, first observed by Virchow[47] in 1853, and frequently since, must be considered retrograde and secondary to an antecedent localized infection. While it is of importance in preventing the healing of an ulcer already formed, it cannot by itself be the primary cause, because ulcer does not regularly follow obstruction of numerous small arteries, [32, 48, 49, 50, 51] not even after ligation of one-third of the arteries to the stomach.[52]

The results of Türck[29] on the production of ulcer in animals by injection and feeding of colon bacilli, possibly applicable in some ulcers, in the light of these findings have little bearing on the chief problem of ulcer of the stomach and of the duodenum in man. Colon bacilli are rarely found in ulcer in man during life, and, if Türck's feeding experiments have a bearing, ulcer of the stomach should occur chiefly in persons with profound malnutrition, the result of improper and insufficient food and unsanitary surroundings.

Since streptococci from certain foci of infection in patients with ulcer tend to produce ulcer of the stomach in animals, might not the frequency of ulcer in the male sex, in certain localities, and during the winter months[53] be best explained on the basis of a high incidence of throat and other infections? Such infections would afford opportunity for streptococci to acquire affinity for the stomach and to gain entrance into the blood-stream.

The ulcers produced in my experiments, like spontaneous ulcers in man, tended to heal in the fundus, and to become chronic in the pyloric portion, the lesser curvature, or the duodenum. While the elective affinity of the bacteria for the gastric mucous membrane is the primary cause of the ulceration, certain contributing factors play a definite rôle in making for the chronicity of the ulcer.

The digestive action of the gastric juice has been repeatedly put forth as a cause of ulcer and as the chief factor in preventing the healing of ulcer. But this is improbable, inasmuch as recent roentgenologic studies [54, 55, 56] have shown that hyperacidity and violent spasms may be present over a period of years from causes outside the stomach without the development of ulcer. Ulceration does not occur along the segment of the stomach thrown into violent spasm directly opposite a

chronic ulcer.   An example of this is shown in Fig. 64, for which I am
indebted to Dr. Carman.   The promptness with which defects in the
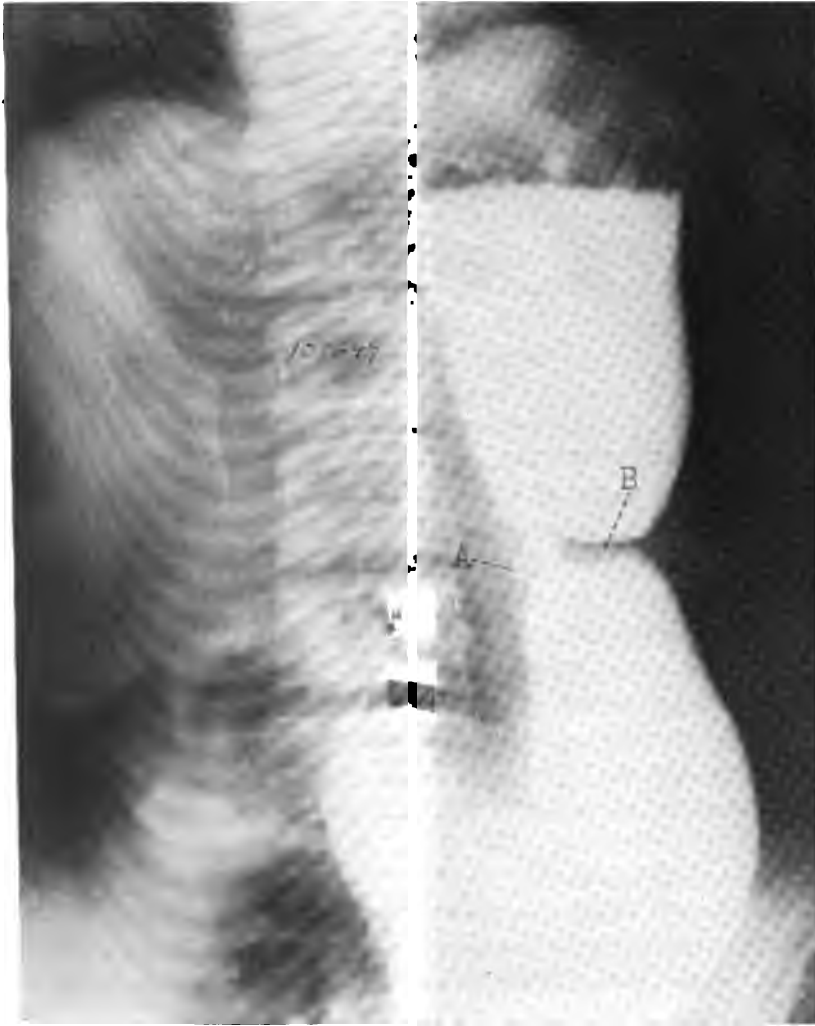
Fig. 64.—Woman aged fifty-two years.   Small, bulb-like projection from lesser curvature in pars media,
at A, which is the crater of a penetrating ulcer.   At B is shown the cramp-like constriction (incisura) of the
circular muscle-fibers.   Operative findings: Gastric ulcer high on the lesser curvature.   Moderate hour-glass
contraction (Carman—Case A-107,649).

mucous membrane of the stomach heal after excision, after injection of
corrosive chemicals, after interference with the blood-supply, and after

'16—6

operations, shows how unimportant is the action of the gastric juice. The fact that ulcer occurs in achylia gastrica[57] also supports this view.

Some ulcers in man may be made to heal when the acidity is reduced by the administration of alkalis, as advocated especially by Sippy,[60] or by the alkaline contents of the duodenum following gastro-enterostomy.* Might not the good effect be due partly to an alkalization of the tissues throughout the body, rather than wholly to local action? The direct digestive action of the hyperacid gastric juice on the floor of the ulcer is believed to prevent the healing. If this is true, chronic ulcer should be found where this action proceeds for the longest time and is most direct; that is, in the acid-secreting portion of the stomach. This is not the case. No matter how prolonged or increased the action of the gastric juice, the fact remains that its corrosive action must be less in the duodenum than in the stomach, and probably is appreciably less in the pyloric segment and in the lesser curvature, the common sites of both experimental and spontaneous chronic ulcers. Something with greater penetrating power than the gastric juice must first damage the cells before they can be digested.

Clinical, roentgenologic,[54] and experimental studies[3, 5, 58, 59] on the physiology of the stomach prove conclusively that ulcers along the lesser curvature, in the pylorus, and in the duodenum are especially prone to be associated with abnormal motility of the stomach and spasm of the pylorus, resulting in delayed emptying, hypersecretion, and hyperacidity. This peristaltic unrest produces mechanical injury, necessarily greatest in the relatively fixed points where chronic ulcer occurs,[62] prevents physiologic rest, and hence serves to maintain the primary infection in the margin of the ulcer, at the same time increasing the liability to secondary infection. This mild, but long-continued, traumatism appears to be of greater importance in preventing healing than the direct corrosive action. Infection and infiltration of connective tissue are favored, resulting ultimately in the calloused, crater-like ulcer, which for mechanical reasons cannot heal, even though the infection is reduced to a minimum or is completely overcome.

This conception is in accord with the results obtained by Bolton,[5] who showed that partial closure of the pylorus delayed the healing of ulcers produced by injections of gastrotoxic serum, but only of those

---

* It should be remembered, however, that freedom from symptoms, and even absence of occult blood in the stool, are no proof that a chronic ulcer has healed; for, as Mayo states,[61] "When supposedly cured patients are operated on during the quiescent interval, the ulcer is not found to be cicatrized, but unhealed. Roentgenograms show the same thing."

that became "septic." It is in accord with Bolton's[63] more recent re-
sults, in which he again showed that delayed healing of ulcer occurred
chiefly in those animals in which the obstruction at the pylorus was so
marked as commonly to cause death, and in those which were given
abnormal concentrations of hydrochloric acid. It is not at variance with
the results of Hamburger and Friedman,[3] who showed that partial
obstruction of the pylorus, resulting in extreme hypermotility and dila-
tation, delayed the healing of ulcers produced by local injection of silver
nitrate, particularly in the pyloric portion. It is in accord with the re-
sults of Durante,[22] who produced ulcers by ligating the splanchnic nerves.
The ulcers shown by him to be chronic present evidence of infection.
If Durante had searched for bacteria, he would undoubtedly have found
them, because in one of the "chronic" ulcers I demonstrated (after the
publication of his paper) not less than 50 cocci and diplococci in the
depths of the tissue which showed leukocytic infiltration; moreover, no
bacteria could be found in the healing ulcer from the same stomach,
which showed no leukocytic infiltration.

Might not this conception best explain the etiologic relationship
to ulcer of the vagotonic or neurotic state in general, as emphasized
especially by Westphal and Katsch,[64] de Kock,[65] Gundermann,[66] and
Eppinger and Hess?[67] Disturbed motility and spasm of the stomach
and hyperacidity occur commonly in neurotic persons.

Moreover, if lesions of the autonomic nervous system are ever a
cause of ulcer, as emphasized by Durante's experiments, then it may be
suggested, in the light of the work by Oftedal and myself on herpes
zoster,[68] and other more recent experiments, that streptococci or other
bacteria or their toxic products may be the cause of the lesions in the
autonomic nervous system.

In support of the view that ulcer of the stomach in the adult is due
to streptococci, it should be stated that Gerdine and Helmholz[69] by the
use of the same methods have not only shown that a recent epidemic
in Chicago of duodenal ulcer in infants was due to streptococci, but on
restudying the sections of the ulcers from a similar epidemic in Berlin,
reported by Helmholz[70] seven years ago, they have demonstrated strep-
tococci in all but 4 of 14 ulcers available.* Furthermore, in a study of

---

* One of the strains from a duodenal ulcer in an infant isolated by them resembled
very closely the strains isolated from ulcers in adults by Sanford and myself. This strain
localized electively in the stomach of rabbits and dogs, producing ulcer, which proved to
be due to local infection after intravenous injections made by Gerdine, by Hardt, and by
myself. Reinjection again produced ulcer.

the etiology of spontaneous ulcer of the stomach in dogs, calves, cattle, and sheep, in conjunction with Dr. Dart and Dr. Henderson (as yet unpublished), it appears that ulcer in these animals also is due commonly to a circumscribed streptococcal infection.

The occurrence of acute ulcer of the stomach and exacerbations of the symptoms in chronic ulcer in connection with foci of infection, the improvement in symptoms following removal of foci of infection, and the development of new ulcers after excision of ulcer in patients in whom chronic suppurating foci have not been removed—all strongly suggest the etiologic relation between remote foci of infection and ulcer. None of these observations, however, proves the etiology of the ulcer. The demonstration of streptococci in foci of infection in patients with ulcer and in the ulcers themselves, and the fact that they localize in the stomach in animals, furnish what seems to me to be the final proof of the etiology.

The conditions under which streptococci acquire affinity for various organs,[68, 71, 72, 73, 74] are still obscure, but of the existence of this affinity of streptococci in diseases there is no question. The fact that in some instances streptococci were isolated from relatively insignificant foci of infection, and the fact of their presence in patients with ulcer over a long period, suggest, as I have already pointed out,[42] that "differences in the host may afford the peculiar type of reaction or that the individual harbors a particular form of focus of infection which is favorable for bacteria to acquire the various elective properties." These observations suggest strongly that while removal of evident foci of infection is important, cure should not always be expected.

The periodic occurrence of exacerbations in symptoms followed by quiescent intervals in chronic ulcer would seem to be best explained on the basis of infection, the former being due to a lighting up of the dormant infection or to reinfection from a focal source when immunity is low, and the latter to quiescence of the infection, the result of heightened local or general immunity.

Summary

The ulcers produced by the injection of streptococci resemble those in man in location, in gross and microscopic appearance, and in that they tend to become chronic, to perforate, and to cause severe or fatal hemorrhage.

Streptococci having a characteristic affinity for the stomach and the

duodenum have been repeatedly isolated from various foci of infection in patients with ulcer and from the ulcers themselves. They tend to disappear from the circulation and do not commonly produce marked lesions otherwise. They have been isolated from ulcers in animals, and ulcer has again been produced on their reinjection. Filtrates of these cultures show no special tendency to produce ulcer. The necessary requirements have been fulfilled to warrant the conclusion that the usual ulcer of the stomach and of the duodenum in man is primarily due to a localized hematogenous infection of the mucous membrane by streptococci.

REFERENCES

1. Quincke, H., and Dättwyler: Cor.-Bl. f. schweiz. Aerzte, 1875, 101. Deutsch. med. Wchnschr., 1882, vi, 79. Quoted by Ewald, C. A.: Diseases of the Stomach, New York, Appleton, 1902, p. 382.

2. Decker: Berl. klin. Wchnschr., 1887, xxiv, p. 369. Quoted by Ewald, loc. cit., p. 384.

3. Friedman, J. C., and Hamburger, W. W.: "Experimental Chronic Gastric Ulcer," Jour. Amer. Med. Assoc., 1914, lxiii, 380–384.

4. Licini, C.: "Ueber experimentelle Erzeugung von Magengeschwüren," Beitr. z. klin. Chir., 1912, lxxix, 462–475.

5. Bolton, C.: Ulcer of the Stomach, London, Arnold, 1913, p. 59.

6. Cohnheim, J. F.: Lectures on General Pathology, London, New Sydenham Soc., 1890, vol. 3, p. 879.

7. Schridde, H.: Verhandl. der deutsch. pathol. Ges., Kiel, 1907, xi, 234. Quoted by Bolton, loc. cit., p. 78.

8. Rehfuss, M. E.: "Experimental Production of Acute Toxic Ulcer of the Stomach," Univ. of Pennsylvania Med. Bull., 1909, xxii, 105–109.

9. Smith, G. M.: "Experimental Study of the Relation of Bile to Ulceration of the Mucous Membrane of the Stomach," Jour. Med. Research, 1914, xxx, 147–183.

10. Sellards, A. W.: "Ulceration of Stomach and Necrosis of Salivary Glands Resulting from Experimental Injection of Bile Salts," Arch. Int. Med., 1909, iv, 502–509. Abstr. Jour. Amer. Med. Assoc., 1909, liii, 24.

11. Elliott, T. R.: "Experimental Formation of Acute Gastric Ulcers," Quart. Jour. Med., 1914, vii, 119–128. Abstr. Jour. Amer. Med. Assoc., 1914, lxii, 576.

12. Friedman, G. A.: "The Influence of Removal of the Adrenals and One-sided Thyroidectomy upon the Gastric and Duodenal Mucosa; the Experimental Production of Lesions, Erosions and Acute Ulcers," Jour. Med. Research, 1915, xxxii, 287–308.

13. Enriquez and Hallion: Compt. rend. Soc. de biol., 1893, 9 sér., v, 1025–1028. Quoted by Bolton, loc. cit., p. 61.

14. Rosenau, M. J., and Anderson, J. F.: "A Stomach Lesion in Guinea-pigs Caused by Diphtheria Toxin and its Bearing upon Experimental Gastric Ulcer," Jour. Infect. Dis., 1907, iv, 1–7.

15. Gioffi: Quoted by Pende, loc. cit.

16. Pende. N.: Fisiopatologia dell' apparte parasimpatico, Milan, Treves, 1906.

17. Gibelli, C.: "La funzione delle capsule surrenali in rapporto col processo di riparazione delle fratture o coll'eziologia dell' ulcera gastrica," Pathologica, 1909, i, 131.

18. Finzi, O.: "Ueber Veränderungen der Magenschleimhaut bei Tieren nach Nebennierenextirpation und über experimentell erzeugte Magengeschwüre," Virchow's Arch. f. path. Anat., 1913, ccxiv, 413–432.

19. Mann, F. C.: "A Study of the Gastric Ulcers Following Removal of the Adrenals," Jour. Exper. Med., 1916, xxiii, 203–209.

20. Elliott, T. E.: "Some Results of Excision of the Adrenal Glands," Jour. Physiol., 1914, xlix, 38–53.

21. Kawamura, K.: "Ueber die experimentelle Erzeugung von Magengeschwüren durch Nervenläsionen," Deutsch. Ztschr. f. Chir., 1911, cix, 540–582.

22. Vedova, R. D.: "Richerche sperimentali sulla patogenesi dell' ulcera gastrica," Suppl. Policlinico, 1900, vi, 1153–1156.

23. Durante, L.: "Contributo alla Fisiopathologia del Nerve Splanevico," Pathologica, 1912–13, v, 631–635. "The Trophic Element in the Origin of Gastric Ulcer," Surg., Gynec. and Obst:, 1916, xxii, 399–406.
24. Ewald, C. A.: Klinik der Verdauungskrankheiten, Ed. 3, Berlin, Hirschwald, 1890–93, vol. 1, p. 122. Quoted by Ewald, loc. cit., p. 382.
25. Charrin and Ruffer: Bull. Soc. anat. de Paris, 5. sér, iii, 18. Quoted by Bolton, loc. cit., p. 61.
26. Chantemesse and Widal: Bull. de l'Acad. de méd. de Paris, 1888, 3. sér., xix, 522. Quoted by Bolton, loc. cit., pp. 61, 63.
27. Wurtz and Leudet: Arch. de méd. expér. et d'anat. path., 1. sér., iii, 485. Quoted by Bolton, loc. cit., p. 94.
28. Rodet, A., and Zaïdmann, R.: "Injections intraspléniques de bacilles d'Eberth et coli," Compt. rend. Soc. de biol., 1900, lii, 1007–1009.
29. Türck, F. B.: "Further Observations on the Etiology and Pathology of Peptic Ulcer," Brit. Med. Jour., 1907, i, 922–926, and other papers.
30. Steinharter, E. C.: "Experimental Production of Gastric Ulcers by Intravenous Injection of Clumped Colon Bacilli," Lancet-Clinic, 1914, cxi, 88–90; Boston Med. and Surg. Jour., 1913, clxix, 81–82.
31. Lebert: Traité d'Anatomie Pathologique, 1857, vol. 1, p. 537. Quoted by Bolton, loc. cit., p. 61.
32. Cohn, B.: Klinik der embolischen Gefässkrankheiten, Berlin, Hirschwald, 1860, p. 523.
33. Letulle: Bull. et mém. Soc. méd. d. hôp. de Paris, 1888, sér. 3, v, 360. Quoted by Bolton, loc. cit., p. 18.
34. Bezançon and Griffon: Bull. et mém. Soc. anat. de Paris, 6. sér., i, 409. Quoted by Bolton, loc. cit., p. 62.
35. Dieulafoy, G.: Textbook of Medicine, Ed. 2, New York, Appleton, 1902, p. 679.
36. Ewald, C. A.: Diseases of the Stomach, New York, Appleton, 1902, pp. 183, 391.
37. Boettcher, A.: Dorpater Med. Ztschr., 1874, v, 148. Quoted by Bolton, loc. cit., p. 60.
38. Dudgeon, L. S., and Sargent, P. W. G.: The Bacteriology of Peritonitis, 1905, p. 58.
39. Hutyra, F., and Marek, J.: Spezielle Pathologie und Therapie der Haustiere, Ed. 2, Jena, Fischer, 1913, vol. 2, p. 331.
40. Rosenow, E. C.: "The Production of Ulcer of the Stomach by Injection of Streptococci," Jour. Amer. Med. Assoc., 1913, lxi, 1847–1850.
41. Rosenow, E. C., and Sanford, A. H.: "The Bacteriology of Ulcer of the Stomach and Duodenum in Man," Jour. Infect. Dis., 1915, xvii, 219–226.
42. Rosenow, E. C.: "Elective Localization of Streptococci," Jour. Amer. Med. Assoc., 1915, lxv, 1687–1691.
43. Rosenow, E. C.: "Transmutations within the Streptococcus-pneumococcus Group," Jour. Infect. Dis., 1914, xiv, 1–32.
44. Mayo, W. J.: "Recurrences of Ulcer of the Duodenum Following Operation," Boston Med. and Surg. Jour., 1914, clxx, 149–151.
45. von Korczynski, E., and Jaworski, W.: "Rundes Magengeschwür und sauer Magenkatarrh," Deutsch. Arch. f. klin. Med., xlvii, 586. Quoted by Ewald, loc. cit., p. 194.
46. Bensley, R. R., and Harvey, B. C. H.: "The Formation of Hydrochloric Acid on the Free Surface and not in the Glands of the Gastric Mucous Membrane," Tr. Chicago Path. Soc., 1913, ix, 14–16.
47. Virchow, R. L. K.: Virchow's Arch. f. path. Anat., 1853, v. 362. Quoted by Bolton, loc. cit., p. 396.
48. Möller, S.: "Die Pathogenese des Ulcus ventriculi mit besonderer Berücksichtigung der neueren experimentellen Ergebnisse," Ergebn. d. inn. Med. u. Kinderh., 1911, vii, 520–569.
49. Pavy, F. W.: Guy's Hosp. Rep., 1867, 3. ser., xiii, 494, and Proc. Roy. Soc., 1863, p. 386. Quoted by Bolton, loc. cit., p. 70.
50. Roth: "Experimentelles über die Entstehung des runden Magengeschwürs," Virchow's Arch. f. path. Anat., 1869, xlv, 300.
51. Litten: "Ueber die Folgen des Verschlusses der Arteria mesenterica superior," Virchow's Arch. f. path. Anat., 1875, lxiii, 289. Quoted by Trotter, L. B. C.: Embolism and Thrombosis, Cambridge, Univ. Press, 1913.
52. Litthauer, M.: "Experimentelle Untersuchungen zur Pathogenese des runden Magengeschwürs," Virchow's Arch. f. path. Anat., cxcv, 317–341. Quoted by Bolton, loc. cit., p. 128.
53. Moynihan, B. G. A.: Duodenal Ulcer, Philadelphia, Saunders, 1910, pp. 106, 251.

54. Carman, R. D.: "The Roentgen Diagnosis of Gastric Ulcer," Amer. Jour. Roentgenol., 1914, i, 233–251.
55. Rieder, H.: "Das Röntgen-Verfahren im Dienste der Pathologie und Therapie des Magen-Darmkanales," Verhandl. d. deutsch. Kong. f. inn. Med., 1912, xxix, 17–41.
56. Holzknecht, G., and Luger, A.: "Zur Pathologie und Diagnostik des Gastrospasmus," Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxvi, 669–694.
57. Eusterman, G. B.: "The Essential Factors in the Diagnosis of Chronic Gastric and Duodenal Ulcers," Jour. Amer. Med. Assoc., 1915, lxv, 1500–1503.
58. Cannon, W. B.: "The Mechanical Factors of Digestion," London, Arnold, 1911.
59. Carlson, A. J.: "Recent Contributions to the Physiology of the Stomach," New York Med. Jour., 1915, cii, 1004–1005, and numerous recent publications in the Amer. Jour. Physiol.
60. Sippy, B. W.: "Gastric and Duodenal Ulcer, Medical Cure by an Efficient Removal of Gastric Juice Corrosion," Jour. Amer. Med. Assoc., 1915, lxiv, 1625–1630.
61. Mayo, W. J.: "Gastric Ulcer," Jour. Amer. Med. Assoc., 1915, lxv, 1069–1073.
62. Stromeyer, F.: "Die Pathogenese des Ulcus ventriculi, zugleich ein Beitrag zur Frage nach den Beziehungen zwischen Ulcus und Carcinom," Beitr. z. path. Anat. u. z. allg. Path., 1912, liv, 1–67.
63. Bolton, C.: "The Part Played by the Acid of the Gastric Juice in the Pathological Processes of Gastric Ulcer," Jour. Path. and Bacteriol., 1915, xx, 133–158.
64. Westphal, K., and Katsch, G.: "Das neurotische Ulcus duodeni," Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxvi, 391–431.
65. de Kock, M. A.: "Maagneurose of ulcus duodeni?" Nederl. Tijdschr. v. Geneesk., 1913, ii, 449–457.
66. Gundermann, W.: "Ueber experimentelle Erzeugung von Magen- und Duodenalgeschwüren," Beitr. z. klin. Chir., 1914, xc, 1–98.
67. Eppinger, H., and Hess, L.: "Sammlung klinischer Abhandlungen über Pathologie und Therapie der Stoffwechsel und Ernährungstörungen," Berlin, Hirschwald, 1910, ix, x.
68. Rosenow, E. C., and Oftedal, S.: "The Etiology and Experimental Production of Herpes Zoster," Jour. Amer. Med. Assoc., 1915, lxiv, 1968.
69. Gerdine, L., and Helmholz, H. F.: "Duodenal Ulcer in Infancy an Infectious Disease," Amer. Jour. Dis. Child., 1915, x, 397–409.
70. Helmholz, H. F.: "The Relation of Duodenal Ulcers to Atrophic Conditions of Infants," Arch. Pediat., 1909, xxvi, 661–673.
71. Rosenow, E. C.: "The Bacteriology of Appendicitis and its Production by Intravenous Injection of Streptococci and Colon Bacilli," Jour. Infect. Dis., 1915, xvi, 240–268.
72. Rosenow, E. C.: "Bacteriology of Cholecystitis and its Production by Injection of Streptococci," Jour. Amer. Med. Assoc., 1914, lxiii, 1835–1836.
73. Rosenow, E. C.: "The Etiology and Experimental Production of Erythema Nodosum," Jour. Infect. Dis., 1915, xvi, 367–384.
74. Irons, E. E., Brown, E. V. L., and Nadler, W. H.: "The Localization of Streptococci in the Eye. A Study of Experimental Iridocyclitis in Rabbits," Jour. Infect. Dis., 1916, xviii, 315–334.

TOXIC GASTRIC HEMORRHAGE *

EGERTON L. CRISPIN

While the development of gastric surgery had proved ulcer to be the most frequent cause of bleeding from the stomach and duodenum, the coincident development of pathology in the living has emphasized the fact that frequently there may be gastric hemorrhage without any demonstrable surgical gastric lesion. The opinion is prevalent among the laity that hematemesis means ulcer requiring operation, and hemorrhage from the stomach is too rapidly accepted by physicians as sufficient evidence to warrant surgery. I wish to call attention to the hemorrhages occurring from other than true surgical lesions, and to the importance of differentiating the causes of bleeding that are medical from those that are surgical.

The calloused ulcer derives greatest benefit from surgery. However, gastric surgery has been too often resorted to without benefit to the patient. Particularly is this true in cases in which hemorrhage was the principal cause for exploration. Often when an abnormal constitutional condition is not obvious, bleeding from the upper gastro-intestinal tract is considered as coming from a so-called hidden or non-symptomatic chronic ulcer, and the patient carries a gastro-enterostomy for ulcer for which there was not sufficient evidence before operation and no evidence at the time of operation. The burden of differentiating hemorrhage due to chronic ulcer from hemorrhage due to non-surgical conditions rests with the internist.

It is true that we occasionally see ulcers, benign and malignant, of which the histories are meager and alone are not sufficient for clinical conclusion. The proportion of these will decrease with a more general knowledge of the varying clinical factors that are helpful in the recognition of the atypical group, and roentgenology will further assist in their diagnosis. Clinical study, supplemented by the diagnostic efficiency

developed in gastric roentgenology, has made it possible to determine the
presence or absence of the bleeding gastric lesions that can be benefited
by surgery in a very large percentage of the cases of hemorrhage from
the stomach.

To designate the oozing of blood from the stomach in the supposed
absence of chronic ulcer Sir Edwin Cooper Perry suggested to Hale
White[1] the term "gastrostaxis," which is similar, etymologically, to
"epistaxis." White[2] advanced the opinion that there might be a clinical
group of this type among young women having pain, vomiting, and
hematemesis, without ulcer symptoms, and in whom spontaneous re-
covery was the rule. The suggestion brought out considerable discussion
in regard to gastric hemorrhages of obscure origin by White,[3] Bolton,[4]
and Hort.[5] As the conditions in which such hemorrhages usually occur
are toxic, the term "toxic gastric hemorrhage" suits our purpose better
and will be used in referring to them here.

Blood that is vomited and tarry stools do not always mean hemor-
rhage from chronic gastric ulcer. Blood from the lungs and pharynx
may be swallowed and later vomited. Bleeding from esophageal varices,
particularly when associated with the toxic state in cirrhosis of the liver,
may be severe and have the appearance of gastric hemorrhage. In the
purpuras, leukemias, and anemias, especially anemias associated with
enlargement of the spleen and liver, there may be severe bleeding from
the stomach. In constitutional diseases and toxemias associated with
hepatic and renal disease it is common to find on necropsy that the gas-
tric mucous membrane is intact, though vomiting of blood occurred
during life. Blood may be vomited during exacerbations in states of
hypertension and in secondary congestions of the liver and spleen.
Endocarditis may be a remote cause of gastric hemorrhage. Also, exuda-
tive erythemic states of the viscera are possible causes of bleeding.[6]
Arteriosclerosis of the abdominal vessels with aneurysmal dilatation and
rupture into the stomach has been reported.[7] During the attacks of
gastric crises in tabes there is often coffee-ground vomitus and at times
bleeding may be severe. Young females may have extensive hemorrhages
with no proof of chronic ulcer and with usually spontaneous recovery.

With infections of the gallbladder and appendix there are occasional
hemorrhages for which no adequate cause in the stomach is found at
operation. In an operated series studied in the Mayo Clinic[8] bleeding
was associated with infections of the gallbladder and gastric symptoms
in 5 per cent., and with appendicitis and gastric symptoms in 2 per cent.

Deaver[9] mentions infections in the fallopian tubes as a causative factor in some cases of gastric hemorrhage. Bleeding from follicles or superficial erosions in the stomach permitting hemorrhage may be secondary to acute infections in the tonsils. Rosenow[10] has shown the association of various streptococcic infections with bleeding from hemorrhagic points and superficial ulcers in the gastric mucosa. These may become so extensive that large patchy areas of the mucosa ooze blood, though when wiped off, individual points are made out with difficulty.

Dieulafoy[11] has called attention to gastric bleeding from the two following varieties of non-chronic ulcer: (1) Simple erosions consisting of mere abrasions of the surface epithelium. These, though so small as to be scarcely perceptible to the naked eye, may give rise to most alarming hemorrhages. At necropsy they may be easily overlooked, but during the course of the hemorrhage the mucous membrane appears to be studded with numerous bleeding points. (2) Exulceratio simplex. The lesions of the type to which Dieulafoy applies this term are somewhat more extensive, and the surface layers are removed to such an extent that the arterioles running under the muscularis mucosæ are exposed. This form may give rise to severe hemorrhages that may even prove fatal. On operation the condition appears as small bleeding fissures, small patchy areas oozing blood, or thick hemorrhagic infiltrations from which blood literally seeps.

Deaver,[9] in discussing hemorrhagic disease of the stomach not associated with, or closely related to, gross ulcer, says: "Excepting extrinsic poisons, I believe the violent congestion of the gastric vessels is primarily dependent on an intra-abdominal, or more rarely remote, focus of infection." This focus of infection he believes is most commonly the appendix or gallbladder. According to Mayo Robson,[12] the gastric lesions after death in some cases of sudden severe hemorrhages, particularly in the young in whom there is no clinical evidence of ulcer, seem altogether inadequate to explain the nature of the serious hemorrhage. It is his opinion also that "capillary oozing or bleeding from arterioles is much more common and accounts for many more cases of gastric hemorrhage than has hitherto been supposed." Hemorrhages of this kind, parenchymatous hemorrhages in the apparently healthy male, hemorrhagic gastralgias, and the large group of variously defined bleedings from the stomach in which there is sudden onset, absence of symptoms, and usually spontaneous recovery, are of infective or toxic origin, and surgery will be of doubtful benefit.

Typical acute gastric ulcer may be the source of repeated hemorrhages if there is erosion of the vessels at its base, but rarely causes fatal bleeding. At operation these ulcers may be shallow and not visible or palpable through the wall of stomach. When secondary to gross infection elsewhere, mucous ulcers may be multiple. Chronic gastric and duodenal ulcers, as a rule, do not bleed copiously. Bleeding from malignant disease usually is small in amount, like that from ulcer, and more or less continuous.

In seeking a cause for gastric hemorrhage a history of ulcer should be sought, and, when necessary, diagnostic evidence should be brought out by every adjunctive means available. If evidence indicating ulcer is not strong, effort should be made to prove or exclude all the numerous conditions that might be underlying causes of the hemorrhage.

In general, surgery offers the best results for ulcer of the chronic calloused type. In this condition the symptoms of ulcer are marked and the patient goes to the physician usually because of the distress from the ulcer rather than because of the hemorrhage. A second group of patients with gastric hemorrhage lays greater emphasis on the bleeding and complains only of gastric symptoms that are more or less indefinite. In such cases effort must be made to determine the presence or absence of calloused ulcer or of a toxic or infective condition as the cause of the hemorrhage. A third group of patients are those who come for examination because of the hemorrhage, but whose gastric symptoms are of minor importance. They believe they have an ulcer, frequently have been told that they have an ulcer, and have often resorted to gastric surgery, which has not prevented subsequent hemorrhages.

Speaking broadly, cases of hemorrhages without gastric symptoms, either before or after surgery, should be considered toxic. The nonsurgical nature of the causative factors, such as the blood diseases and secondary congestions, are usually easy to determine. Medical observation will further develop the exact nature of many hemorrhages of the toxic group, and relegate them to their proper medical sphere. When an infective source, either intra-abdominal or remote, is found, the possibility of an association between the gastric hemorrhage and this infected atrium should be considered. In many such cases the hemorrhage is probably toxic. When medical observation determines the presence of abnormal constitutional states, such as diseases of the blood, renal toxemias, disproportional varices, pathologic vascular tensions, multiple angiomas, syphilis, or tuberculosis, the hemorrhage should be considered

of toxic nature. Correction, when possible, of the underlying conditions, and waiting, rather than surgery, is advisable. Any surgery in these cases should be only in the nature of exploration without promise as to results. Spontaneous hemorrhages occurring in young women, and parenchymatous hemorrhages in which evidence does not point to chronic ulcer, should also be considered toxic. They are not surgical; spontaneous recovery is the rule.

Patients giving a history of repeated severe hemorrhages over many years, with an ulcer history, which, though not clear-cut, is strengthened by adjunctive evidence, and in whom no constitutional cause can be found, should have an exploratory operation. In such cases the hemorrhage is probably due to a surgical condition. Well-nourished patients who have had one or a few hemorrhages, and for whom the clinical or contributory data are very poor, may be considered toxic until medical observation proves the absence of a constitutional condition as a factor, or time brings out evidence of ulcer. If surgery is indicated at all for gastric hemorrhages occurring in the presence of intra- or extra-abdominal infection and accompanied by indefinite gastric symptoms, it should be applied to the focus of infection rather than to the stomach.

Patients who have had repeated hemorrhages for many years, who are past middle life, whose general appearance is below par, and of whom the history and evidence of ulcer are indefinite, should also be carefully studied for toxic causes. The following abstracts of histories will serve to illustrate various types of gastric hemorrhage.

Clinical Evidence Alone Insufficient for Ulcer. Exploration Because of Positive Roentgen Findings

CASE 146,581.—M. C. B., traveling salesman, aged fifty-two years. Examined November 30, 1915. Patient had been having hemorrhages from the bowel, black and tar-like, for thirty years; in all, about 20; in bed after each attack. The last hemorrhage occurred in June, 1915. Three hemorrhages in 1913. No clear-cut gastric history, though he had had distress for days at a time, and on a few occasions for a couple of weeks. Food relief variable; never used soda; never had colic. Present trouble with stomach of about two weeks' duration. He dieted for two years but did not obtain relief. In present attack he had had a little distress at night, varying from 11 P. M. to 5 A. M., and some distress after meals. Most of the hemorrhages "have come out of a clear sky when he was feeling his best." Epistaxis frequent in youth, but never put him to bed.

Examination.—A healthy-looking man, 5 feet, 9 inches in height,

weighing 145 pounds; no weight loss. Mucous membrane somewhat pale. Multiple, pea-sized, raspberry angiomas over body. Hemoglobin, 70 per cent. Gastric analysis: Acids, 58, 44, 14; no food remnants. Wassermann negative. Coagulation time, three minutes. Blood-pressure, 128, 90. Eye-grounds negative. Urine negative. Proctoscopic findings negative. Roentgen findings: Cap deformity; duodenal ulcer.

A history covering thirty years with slight symptoms except for bleeding, clinical absence of obstruction at the pylorus, and the angiomas over the body, made diagnosis doubtful. An exploratory operation was performed because of the roentgen evidence. A duodenal ulcer was found ½ inch below the pylorus.

Clinical and Adjunctive Evidence Insufficient for Ulcer. Considered Toxic and Not Now Surgical

CASE 141,079.—T. A. C., advertising manager of a newspaper, aged fifty years. Examined September 15, 1915. Patient had been in the habit of eating fast; worked hard; burned the candle at both ends. Formerly a printer. Twenty-five years ago he had anemia, which he thought was due possibly to lead poisoning. In the last twenty-five years he had had a few attacks of gastric trouble lasting a week or two. Symptoms meager. In October, 1914, he fainted one day while in the toilet; soon vomited food and blood. Vomited clots three times within a short period. Had tarry stools for the following three or four days. Was put on a von Leube diet and rapidly regained his health; well since. Came for examination eleven months later because an ulcer had been diagnosed at the time of the hemorrhage. No symptoms since hemorrhage except a little discomfort, without food relation, in the left hypochondrium.

Examination.—Height, 5 feet, 10½ inches; weight, 195 pounds; no weight loss; skin somewhat highly colored. Blood-pressure, 178, 100. Gastric analysis: Acids, 66, 56, 10; no food remnants. Hemoglobin, 89 per cent. Differential blood count normal. Coagulation time, eight minutes. Wassermann negative. Negative fundi. Urine showed a few hyaline casts. Roentgen findings: Stomach indeterminate.

On account of lack of evidence of ulcer, and because of the blood-pressure, urine findings, coagulation time, and patient's generally well-nourished condition, diagnosis was made of toxic hemorrhage. He was advised about caring for his general health, and sent home for observation.

Negative Gastric Exploration. Constitutional State. Visceral Angio-neurotic Edema Believed to be Cause of Bleeding

CASE 101,588.—W. H. S., paper-hanger, aged forty years. Examined March 4, 1914. This patient had been urged a number of times to have operation for gastric ulcer. He had had gastric trouble intermittently for twenty-three years. When seventeen, cramps were so severe

as to double him up. He used to tie a towel tight around his waist, and
a number of times was rolled over a barrel to relieve the cramping pain.
These attacks came frequently for a few weeks and then disappeared for
weeks or months. Only occasional trouble between the ages of twenty
and thirty. In an attack when about thirty-one he vomited a large hand-
ful of clots of blood. No clear-cut food relation to gastric pain. Present
attack, three weeks. No regularity. For three months has had most
marked angioneurotic disturbances. Large plaques came out on his
skin each night. Roentgen findings: "Lesion of the stomach at or near
the pylorus." The patient had angioneurotic swellings. At exploration
(C. H. Mayo) neither lesion nor cause for hemorrhage was found in the
stomach. The gallbladder, showing doubtful pathology, and the appen-
dix were removed.

The attacks of pain have continued since operation without any
material change in nature. They are regarded as visceral manifesta-
tions of angioneurotic edema. Because of the constitutional condition,
the hemorrhages may be considered toxic.

*Young Woman. Hemorrhage. Treatment for Ulcer. No Symptoms or
Evidence of Ulcer. Spontaneous Recovery*

CASE 147,636.—Miss A. R., aged twenty-one. Examined December
11, 1915. She complained of gastric trouble and menorrhagia. Eighteen
months before a severe hemorrhage occurred in the stomach; melena
persisted for a number of days. She was put to bed and kept on a milk diet
for seven months. Her physician said the bleeding came from an ulcer
in the stomach. She had been away at school, had eaten irregularly and
injudiciously a large amount of candy; enjoyed social activity, dancing,
tennis, etc. Indefinite distress in the stomach began a month or two
before the hemorrhage—about the middle of the school year. Stomach
always tender; with pain and soreness after eating ordinary foods;
never free periods. No food relief. Menstruation irregular—increased
flow for three years; for two weeks at each period a profuse flow. Patient
said she had had grip three or four times. Wrenched her back four years
ago, and it "had been sore ever since."

Examination.—A thin, somewhat pale young girl. Very nervous.
Weight, 104 pounds. Blood-pressure, 100, 78. Urine negative. Hemo-
globin, 89 per cent. Gastric analysis: Acids, 20, all combined; no food
remnants. Roentgen findings: Stomach negative. At the hotel the
patient ate everything and forgot all about her stomach.

Because of the hemorrhage she firmly believed that she had an ulcer,
as did her mother and her brother, a physician. Her physician had ad-
vised operation for ulcer. The seven months in bed on ulcer treatment
had made her a marked neurasthenic. There was neither clinical nor
laboratory evidence of ulcer. Patient was told that there was no evidence
of chronic ulcer and operation was not advised.

Gastric Attacks With Hemorrhages Following Tonsillitis

CASE 145,217.—Mrs. R. T., aged twenty-four years. Examined November 8, 1915. Epigastric pain; hemorrhages from stomach. She has had repeated attacks of tonsillitis and rheumatism. Distress in stomach at times for eight years. Cramp-like pains lasting five or ten minutes, associated with nausea. Vomited during the first five years, but seldom vomited food. Has had numerous hemorrhages from stomach in one of which she said she lost a quart of blood. Gastric symptoms lasted ten days to two weeks; she was then relieved for a period of months. No definite food relationship. The pain was present even when a strict diet was maintained. About three attacks of tonsillitis each winter. Gastric attacks always followed tonsillitis. In a remission four weeks before there was a hemorrhage from the stomach.

Examination.—Short, soft, systolic blow heard at cardiac apex. Blood-pressure, 122, 82. Pulse, 68. Temperature, 99.2° F. Urine negative. Hemoglobin, 70 per cent. Gastric analysis: Acids, 48, 28, 20. Roentgen findings: Chest negative; stomach indeterminate. *Consultant's Note:* "Not typical ulcer. History suggests superficial type of acute lesion with hemorrhage. The frequency with which tonsillitis has preceded attacks is interesting." Tonsillectomy by Dr. Matthews. Culture from tonsils by Dr. Rosenow showed streptococci, and animals injected showed multiple hemorrhages and superficial ulcers of the stomach due to streptococci. Hence these hemorrhages, which seemed to be toxic, were apparently due to localized hematogenous infections of the mucous membrane of the stomach following tonsillitis.

Gastric Symptoms With Hemorrhages. Exploration: Chronic Appendicitis. Negative Gallbladder and Stomach

CASE 126,387.—E. G. P., contractor and builder, aged forty-six years. Examined March 12, 1915. This patient had had myalgias, followed by ecchymoses that put him in bed for three or four days. For fifteen years he had had trouble with his stomach, which came on in spells formerly lasting for months. Trouble now continuous. Had had some food relief and relief by alkalis and vomiting. A burning sensation was felt in the stomach usually from 10 to 11 P. M. Hemorrhage from the stomach. Vomited a large quantity of blood during a period of two days. Four months ago had another hemorrhage, and at that time tarry stools. Described pain radiation as being "most anywhere" in the upper abdomen. Patient very nervous; continuous headache for last two months.

Examination.—Under weight. Blood-pressure, 150, 105. Hemoglobin, 88 per cent. Coagulation time, five minutes. Wassermann negative. Moderate right pyelitis, proved by ureteral catheterization. Gastric analysis: Acids, 34, 22, 12; no food remnants. Exploration for peptic ulcer (W. J. Mayo). *Findings at operation:* "Subacute appendicitis. Appendicitis apparently would account for symptoms, as it was

rather unusually well marked. Gallbladder and duodenum normal. Gallbladder somewhat adherent, but empties easily and contains no stones." Appendix removed. After negative exploration of upper abdomen the hemorrhages were believed to be gastrotoxic—secondary to the infection in the diseased appendix.

Gastric Symptoms, Hemorrhage, Came for "Ulcer." Exploration: Cholecystitis and Pancreatitis. Negative Stomach and Duodenum

CASE 124,020.—Mrs. N. M., aged thirty-six years. Examined February 8, 1915. Trouble with stomach began four years ago. First attack, four months. One free period of three years. Second attack began one year before; was ill nine months. She had pain nearly continuously except when eating. Vomited sour water. Once she had delayed vomiting. Slight food relief. Soda relief formerly. Has sharp cutting pain in left epigastrium, for which her physician had given morphin. Tarry stools. Coarse and sour foods caused distress. Patient referred to the Mayo Clinic with a diagnosis of ulcer with hemorrhage.

Examination.—A very neurotic, fairly well-nourished woman. Area complained of, the left epigastrium. Slight tenderness to deep pressure in right lower abdomen. Blood-pressure, 125, 80. Urine negative. Hemoglobin, 85 per cent. White blood-cells, 7000. Gastric analysis: Acids, 28, 12, 16; no food remnants. Roentgen findings: Stomach indeterminate. The physician at home and the patient were sure that ulcer was the cause of her distress and bleeding. She was under observation a week, then sent for exploration of the stomach, the gallbladder, and the appendix. Cholecystectomy and appendectomy were done. *Findings at operation* (E. S. Judd): "Definite chronic cholecystitis and chronic pancreatitis. Head of pancreas twice its normal size; chronic appendicitis; stomach and duodenum negative."

Negative Exploration. Toxic Constitutional Condition. Cardiorenal Syndrome With Transient Hypertension

CASE 135,561.—H. R. T., bank cashier, aged sixty years. Examined July 17, 1915. Patient had had hemorrhages from the bowels (tarry stools) seventeen years, ten years, and five years ago. In September, 1914, also vomited blood; collapsed. In years past had to be careful of his diet and had intermittent discomfort. A clear history was difficult to obtain. A diagnosis of ulcer was made after each hemorrhage. In the fall of 1914 a gastrojejunostomy was done for "ulcer on anterior duodenal wall 1 inch below the pylorus." Four weeks before coming for examination he had collapsed, and the next day had profuse tarry stools.

Examination.—Five feet, seven inches in height; weighed 130 pounds; underweight. Appeared weak and had marked pallor. Some bagginess under eyes. Sclera pearly; looked nephritic. Heart 5 inches to left.

Diastolic murmur at aortic area. Blood-pressure, 185, 85. Hemoglobin, 45 per cent. Coagulation time, six minutes. Differential blood count normal. Gastric analysis: Acids, 64, 54, 10; no food remnants. Wassermann negative. Old patches of hemorrhages in fundi. Phenolsulphonephthalein functional test, 43 per cent. in two hours. Roentgen findings: Gastro-enterostomy functioning; otherwise negative. Patient gained on ulcer diet. Was kept under observation for three weeks. Believed to be gastrotoxic, but because of reported presence of ulcer at the time of gastro-enterostomy done elsewhere, and in order to clear up the nature of the condition, an exploratory operation was performed (W. J. Mayo). *Surgical report:* "Two inches of the stomach and two inches of the duodenum were resected. Gastro-enterostomy in good condition. Site of supposed ulcer on duodenum resected. Patient in wretched condition." *Pathologic report:* Pyloric ring of stomach normal; on section, scar of ulcer could not be found.

The patient gained rather slowly after operation. About three months later he had a very severe hemorrhage. Was found unconscious in a pool of blood in the bathroom. A letter from his home physician stated that a blood-pressure of 250 systolic had been recorded a few days before the hemorrhage. It is probable that all the bleedings were the result of a constitutional state, toxic in type, and of a nature that surgery could not benefit.

SUMMARY

Toxic gastric hemorrhage is essentially a medical condition. Hemorrhage does not always mean chronic ulcer. Surgery should be resorted to for the calloused type of ulcer, and for this type only will it give the best results. Recognition of the true cause of hemorrhage from the upper gastro-intestinal tract is sometimes most difficult. At times evidence will warrant exploration to prove or exclude peptic ulcer as a cause. The presence of a constitutional disease without sufficient evidence of ulcer makes medical observation and study rather than surgery advisable. In cases of hemorrhage of obscure origin search for infected foci should be made and the possibility of their association with the cause of the hemorrhage should be considered. In addition, studies of blood diseases associated with bleeding, and further studies in blood-pressure, with recognition of transient hypertensive states, will help to define and separate hemorrhages having their origin in surgical ulcer from gastric hemorrhages of acute infective and toxic origins.

REFERENCES

1. White, W. H.: "Gastrostaxis or Oozing of Blood from the Mucous Membrane of the Stomach," Lancet, 1906, ii, 1189–1195.
2. White, W. H.: "Are Not Some Patients Said to be Afflicted with Gastric Ulcer Really Suffering From a Different Disease?" Lancet, 1901, i, 1819–1820.

3. White, W. H.: "Gastrostaxis," Brit. Med. Jour., 1910, i, 1347–1348.
4. Bolton, C.: "Does Gastrostaxis Exist as an Independent Disease?" Brit. Med. Jour.,
   1910, i, 1221–1224.
5. Hort, E. C.: "Gastrostaxis," Brit. Med. Jour., 1910, i, 1443.
6. Crispin, E. L.: "Visceral Crises in Angioneurotic Edema," St. Paul Med. Jour., 1916,
   xviii, 127–133.
7. Hood, D. W. C.: "Hematemesis Due to Arteriosclerosis of the Gastric Vessels,"
   Lancet, 1912, ii, 1177.
8. Eusterman, G. B.: "The Essential Factors in the Diagnosis of Chronic and Duodenal
   Ulcers," Jour. Amer. Med. Assoc., 1915, lxv, 1500–1503.
9. Deaver, J. B.: "Gastric Hemorrhage," Surg., Gynec. and Obst., 1914, xviii, 294–299.
10. Rosenow, E. C.: "Elective Localization of Streptococci," Jour. Amer. Med. Assoc.,
    1915, lxv, 1687–1691.
11. Dieulafoy, Quoted by Robson, *loc. cit.*
12. Robson, A. W. M.: "Discussion on the Surgical Treatment of Hematemesis," Lancet,
    1902, ii, 1626–1630.

DUODENAL ULCER WITH ACHLORHYDRIA *

EGERTON L. CRISPIN

In duodenal ulcer the total and free acids are usually high. The free acid frequency has a higher relative proportion than normal. Subnormal acidities are occasionally recorded. In gallbladder disease subacidity and achlorhydria are quite common. When the clinical history is not distinctive of either lesion, and particularly when there are no direct roentgen findings, the gastric analysis is used to influence the weight of evidence in making the diagnosis. Gastric analysis showing an achlorhydria with the usual test-breakfast technic should not too strongly prejudice against a diagnosis of duodenal ulcer, if the evidence given by the patient indicates ulcer.

The following is a brief review of the history of 11 cases in the Mayo Clinic of operatively proved duodenal ulcer in which the gastric analysis showed an absence of free hydrochloric acid.†

The analyses were made by the routine technic used in the Clinic. Patients sent for gastric analysis are instructed to eat an evening meal of bread, meat, potatoes, etc., to be followed later by about 20 raw raisins. In the morning they are given a test-breakfast consisting of 30 gm. of arrowroot biscuit and 400 c.c. of water. The water is served in two portions—one warm and the other cold. The test-breakfast is withdrawn after from fifty to sixty minutes, and any remnants of the evening meal are noted. The gastric content is filtered and titrated with phenolphthalein and dimethylamidoazobenzol. When the amount of free hydrochloric acid is below 20, Günzberg's test is done. This is delicate to 0.005 per cent. for free hydrochloric acid. The Rehfuss acidity curves and short-time motor meals are not included as part of the routine examination.

Ten of the 11 patients in this series were males. The one female,

aged thirty-seven, was the youngest. The oldest patient was sixty-six. The average age was fifty-four years. Four of the patients had used alcohol moderately, *i. e.*, 1 on a basis of 0 to 4. Seven had been moderate users of tobacco. In no case was there history or evidence of syphilis. In all there was weight-loss, the greatest being 94 pounds, the least 5 pounds, and the average, not counting the very excessive loss of 94 pounds in one case, 15 pounds.

It is interesting to note that, as regards previous illnesses, four of the patients (36 per cent.) had had typhoid fever on an average of twenty-four years before. Three of the patients had had abdominal operations; in two the appendix had been removed eight and six years before, respectively; the third patient had been operated on for gall-stones four years before; stones were not found; the gallbladder was drained and the appendix removed.

The average duration of gastric history in these cases was 6.9 years. The duration of attacks when the patients presented themselves for examination had varied from three weeks to five months. In three instances there was complaint of continuous trouble for a year or more; in nine there was a history of spells and free periods. The appetite was variable, being given by different patients as poor, fair, and good. In only one case was a cause ascribed for the attack; in this it was attributed to chill or cold.

All the patients had pain or distress. In two instances it was located in the stomach, in five in the epigastrium, in one in the left epigastrium, in one in the right epigastrium, and in two in the epigastrium and right costal margin and through to the back. The intensity varied from a dull aching to a burning, gnawing pain lasting until food was taken. The time of pain or distress was variable, beginning from one-half to four hours after meals. Night pains were recorded in three instances. The methods used to control distress were given as food taking in 8 cases, alkali in 6, gastric lavage in 2, and morphin in 1. The type of pain indicated perforation in one case. Nine patients gave a history of vomiting, varying in character from hot sour water to delayed vomit. Two patients had hematemesis. Nine complained of gas, belching, and bloating. Eight were constipated; three had had diarrhea; and three reported blood from the bowel.

In none of these cases was free hydrochloric acid found in the gastric content. The lowest acidity was 4-0-4, the highest, 38-0-38; and the average, 15-0-15. Food remnants from the evening meal were with-

drawn with the test-breakfast content in 6 of the cases. The largest amount of retention was 1200 c.c.

Ulcer was diagnosed clinically in 6 cases; ulcer or cancer, with a question mark, in 2; cancer of the pylorus in 1; and cancer of the stomach in 1. One case was marked "for exploration." Gallbladder disease was recorded in the clinical diagnosis in 3 cases and carcinoma of the pancreas in 1. Disease of the appendix was recorded as a part of the diagnosis in one instance. The roentgen examination, made in 10 of these cases, was correct in 5, indeterminate in 2, negative in 1, and in error in 2.

In operating in these cases of duodenal ulcer it was found that 1 was associated with empyema of the gallbladder; 2 had perforated; in 3 there were also gastric ulcers (in two instances on the posterior wall, and in one on the lesser curvature). In 5 cases there was no disease other than the duodenal ulcers in the upper abdomen. In 6 of the cases marked obstruction of the duodenum was found at operation. In 1 there were two ulcers on the anterior surface of the duodenum. In 5 of the 11 cases the appendix was removed at the time of operation. Because of the ulcers, a gastro-enterostomy was done in all.

SPASM OF THE STOMACH AND DUODENUM FROM A ROENTGENOLOGIC POINT OF VIEW*

RUSSELL D. CARMAN

- - -   -

The roentgenologic study of disease in the gastro-intestinal tract requires a thorough acquaintance with spasm of the visceral musculature, its numerous manifestations and their comparative importance. Though recognized early by roentgen workers, spastic phenomena deserve increasing attention and study because they are relatively common and occasionally very perplexing.

Organic deformity of the luminal contour is the principal roentgenologic sign of disease in the digestive tube, not only revealing a lesion, but directly showing its location, its size, and often its character. It shows an addition to or a subtraction from the luminal outline when brought into view by the administration of substances opaque to the roentgen ray. Striking examples of organic deformity are seen in the filling defect resulting from gastric cancer and the niche or barium-filled crater of chronic penetrating gastric ulcer, the diagnostic value of which must be conceded.

Many roentgenologists refuse to make a diagnosis in the absence of these signs, and claim that "sign complexes," made up of indirect manifestations, are of no value. This view is far too radical, for if roentgen diagnosis were limited only to cases in which these direct indications are noted, many lesions of the alimentary canal would pass undiscovered. Often we are obliged to rely on more remote phenomena for diagnosis, such as alterations of motility, tonus, and peristalsis.

All of these can be materially affected by spasm. Further, we are more or less dependent on changes of contour, spastic in nature, but set up by an intrinsic lesion, as, for example, the incisura and spasmodic hour-glass of gastric ulcer. Still further, and even more important,

we encounter and must be able to recognize spastic deformity of outline produced reflexly by extrinsic conditions, remote from the deformed organ. Such deformity may deceptively simulate the distortion produced either directly or indirectly by an intrinsic lesion. Thus the roentgenologist is called on to deal with two types of spasm. We can speak of one type as intrinsic and the other as extrinsic. One is often a help to diagnosis; the other often a hindrance.

Fig. 65.—Incisura, *a*, and prepyloric spasm, *b*, due to gastric ulcer. No visible niche. Both spasms were seen during the vertical screen examination, and persisted after belladonna was given.

Spasm of the Stomach

The favorite playground of spasm, whether of intrinsic or extrinsic origin, is the stomach. Spasm of the stomach, arising from an intrinsic lesion, is generally produced by ulcer, less often by cancer.

Three forms of spasm due to gastric ulcer may be distinguished: (1) The incisura or hour-glass stomach; (2) diffuse spastic distortion, and (3) spasm of the pyloric sphincter.

1. The incisura is a spastic contraction of the circular muscle-fibers in the plane of the ulcer, and shows as an indentation of the opposite curvature. Usually narrow, but of variable depth, persistent and per-

manent as to situation, it suggests at once the nature of the lesion and
points toward its site. The cavity of the ulcer itself may often be seen
as a niche or pocket, but sometimes neither can be distinguished. In
the latter event the incisura either alone or in combination with other
functional disturbances may guide to the diagnosis which otherwise
could not be made.

When the incisura is deep, the stomach is bilocular, and the examiner
may either describe it as an hour-glass stomach, or emphasize only the

Fig. 66.—Extensive prepyloric spasm due to gastric ulcer. Niche of ulcer seen at a. Pyloric end, b, showing
spasm.

incisura. In other instances the width and depth of the constriction are
so extreme that the characteristics of a typical incisura are lost, and a
pronounced hour-glass form is seen.

2. Gastric ulcer often gives rise to a diffuse spasm affecting a con-
siderable extent of the pyloric segment, whether the ulcer be situated in
this region or higher up in the stomach. The stomach, well outlined in
its upper portion, shades off into a poorly filled, vaguely outlined antral
area, which may resemble the filling defect of a pyloric cancer.

3. An ulcer situated in the pyloric segment is frequently accompanied

by retention from the six-hour meal. Ulcers situated well away from the pylorus are occasionally associated with a six-hour retention. This retention has been variously ascribed to reflex pylorospasm, to impairment of peristalsis by the ulcer, to gastric hypotonus, and to pyloric spasticity excited by hyperacidity. Be this as it may, we have seen cases of gastric ulcer in which a retention from the six-hour meal was the only discoverable sign. This, taken alone, was, of course, insufficient for diagnosis.
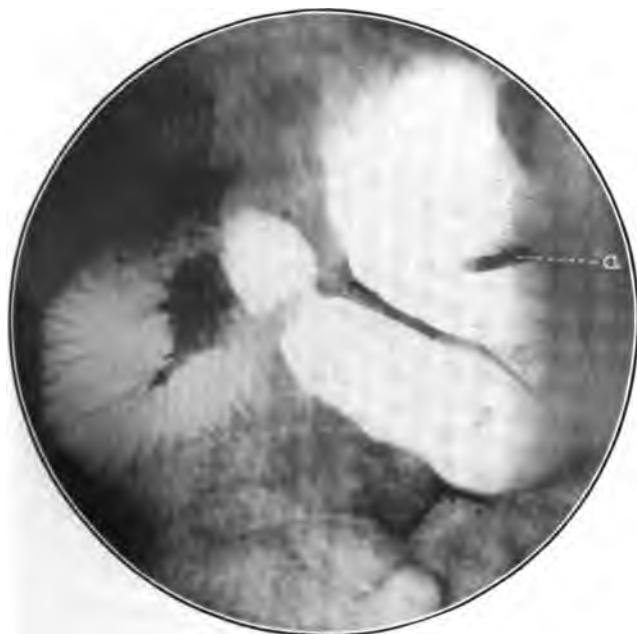
Fig. 67.—Incisura-like spasm at *a*. No other roentgen findings. Small mucoid cancer, lesser curvature, posterior wall, found at operation.

Cancer of the stomach, aside from the organic filling defect produced by the tumor mass, may also produce more or less spastic distortion of the gastric contour. For example, a cancer involving only a portion of the lesser curvature may be accompanied by a spastic indrawing of the greater curvature opposite the lesion. When present, it is usually of considerable width, and exaggerates the luminal narrowing produced by the tumor. The examiner is quite apt to regard this indrawing as a part of the organic filling defect, but generally it is sharply sketched, while the filling defect shades off gradually. The matter becomes of importance in forming an opinion as to the probable extent of the cancerous

invasion. Quite recently we have encountered a case in which a small mucoid cancer of the lesser curvature, posterior wall, was attended by a decided incisura. The growth, because of its location and small size, did not of itself produce any definite deformity, and the roentgen diagnosis of a lesion was based solely on the persistent spasm.

All of the above-described spastic phenomena are intrinsic; that is, they originate from lesions of the stomach itself. Quite as frequent, perhaps even more frequent, are the extrinsic spasms—those which
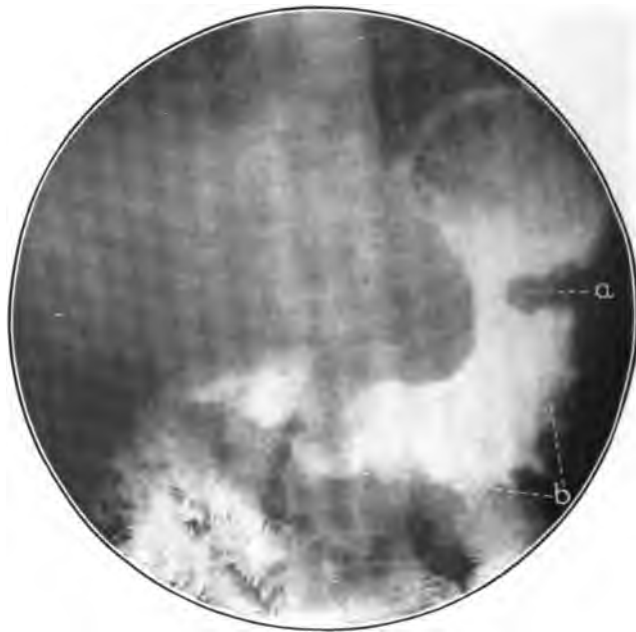
Fig. 68.—Broad deep incisura, a, and extensive spasm throughout greater curvature, b. No other roentgen signs. Small cancer, posterior wall, found at operation.

accompany abnormal conditions outside the stomach, often remote from it.

One of these spasms takes the aspect of an incisura much like that of gastric ulcer, but usually it is either intermittent or progresses toward the pylorus like a gigantic peristaltic wave. Occasionally a marked hour-glass form of the stomach, which may either relax suddenly or persist throughout the entire period of examination, has an extrinsic cause, though it is difficult for the examiner to abandon his suspicion of a lesion in the stomach. Duodenal ulcer is occasionally associated with

a gastric incisura or an hour-glass stomach.   Equally misleading is a
spastic filling defect of extrinsic origin, occurring more commonly in
the pyloric end of the stomach, and resembling a pyloric cancer or the
diffuse spasm provoked by a gastric ulcer.

In many instances, after a barium meal, none of it is seen to pass
the pylorus for several minutes.   At operation a cholecystitis or a chronic

Fig. 69.—Spastic prepyloric narrowing, a.   At operation: Cholecystitis; strawberry gallbladder.

appendicitis is found, but no lesion of the stomach.   In such a case there
is evidently a pylorospasm, not necessarily in the clinical sense, but a
spasticity of the pyloric sphincter for which the only explanation that
can be offered is the diseased gallbladder or appendix.   Sometimes the
entire pyloric third of the stomach is shrunken to a stiff, narrow tube
which may be palpable to the examining fingers.   The tube projects like
a spigot from the well-expanded fundus, and shows a striking likeness to

the canal through a pyloric tumor. In this species of spasm disease of the gallbladder is frequently found.

The foregoing extrinsically caused spastic manifestations are all localized or regional. But spasm from an outside source may affect the entire gastric musculature, giving rise to total gastrospasm. Total gastrospasm is characterized by a gastric hypertonus which far exceeds physiologic limits—renders the stomach contracted, tense, and inactive. The gas-bubble is small. Little secretion is present, as a rule. Canalization is delayed, the first swallows of the meal being held high up in the fundus. With continued filling, the ingesta finally reach the pylorus and the stomach assumes its normal form, but is diminutive in size. It lies high up under the left costal arch and entirely to the left of the spine. On further addition to the gastric content the fundus expands to accommodate it, but the pyloric portion remains narrow. Peristalsis is usually absent altogether, although there may be a few faint, irregular waves. The gastric contour lacks the smooth regularity of the normal filled stomach. Mobility and flexibility are not only actually lessened somewhat by the stiffened spastic gastric wall, but, by reason of the high sheltered position of the stomach, it often seems to be practically immobile and inflexible. The pyloric sphincter, contrariwise, may remain steadily open, and there is an early free and continuous exit of the barium meal. The whole picture is much like that of extensive gastric cancer, and might easily deceive the unwary examiner. It should be reiterated that the frequent resemblance of reflected gastrospasm, whether local, regional, or total, to the filling defect of a gastric cancer or ulcer, makes its recognition imperative, not only by the novice, but by the expert as well. It follows that in the presence of what seems to be a filling defect, precautions should always be taken to exclude the possibility of spasm.

The causative agents of extrinsic gastrospasm are hard to prove definitely. Mention has been made of the association of duodenal ulcer and disease of the gallbladder and appendix with gastrospasm. These associations are so frequent that the assumption of an etiologic relationship seems only rational. Others have noted, as probable causes, hysteria, pancreatic disease, tabes, arteriosclerosis affecting the abdominal viscera, renal and ureteral calculi, uremia, and poisoning by lead, nicotin, and morphin. A condition imitating gastrospasm is a distortion of the stomach produced by strong retraction of the abdominal wall. This is usually seen in frightened or nervous patients, who are
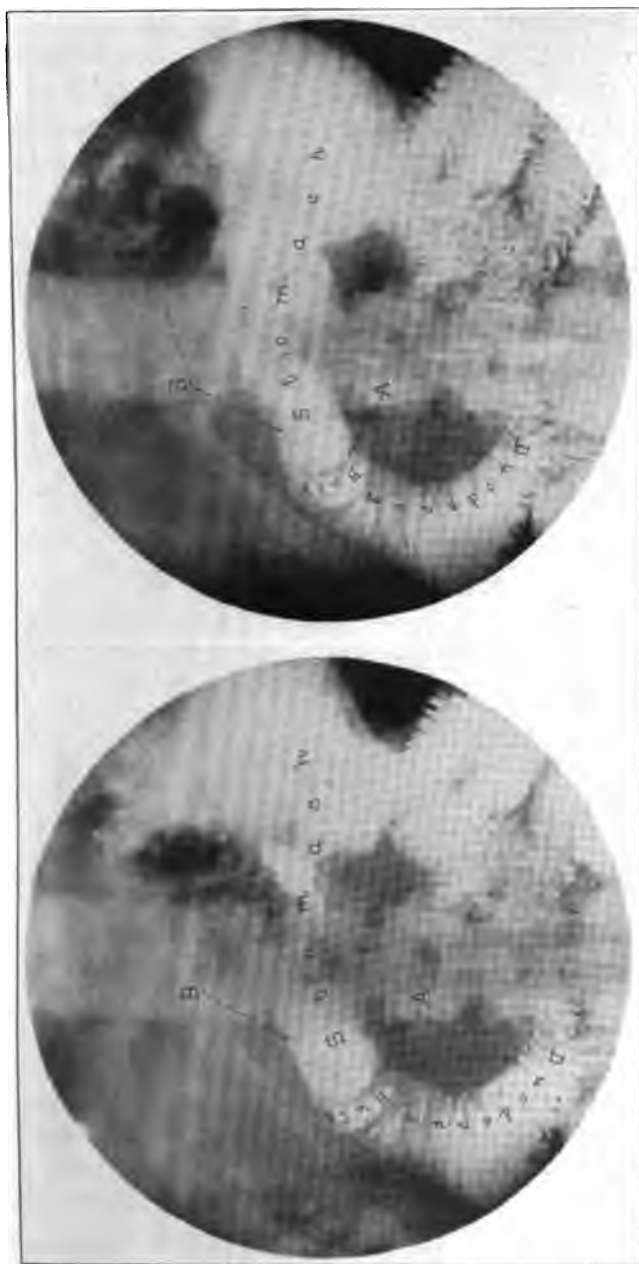
Fig. 70.—Total gastrospasm. The gastric contour is distorted as though by extensive filling defects in the body of the stomach and lesser curvature, *B*. The pylorus, *A*, is gaping. At operation the stomach was found to be normal, but there was definite disease of the gallbladder and appendix.

made apprehensive by the procedures necessary to a roentgen examination. By quieting the patient's fears and persuading him to relax, the stomach will usually assume its normal form.

Differentiation.—Given a case which shows an irregularity of the gastric contour, the examiner must determine, as far as he can, whether the distortion is due to: (1) An organic lesion producing deformity;
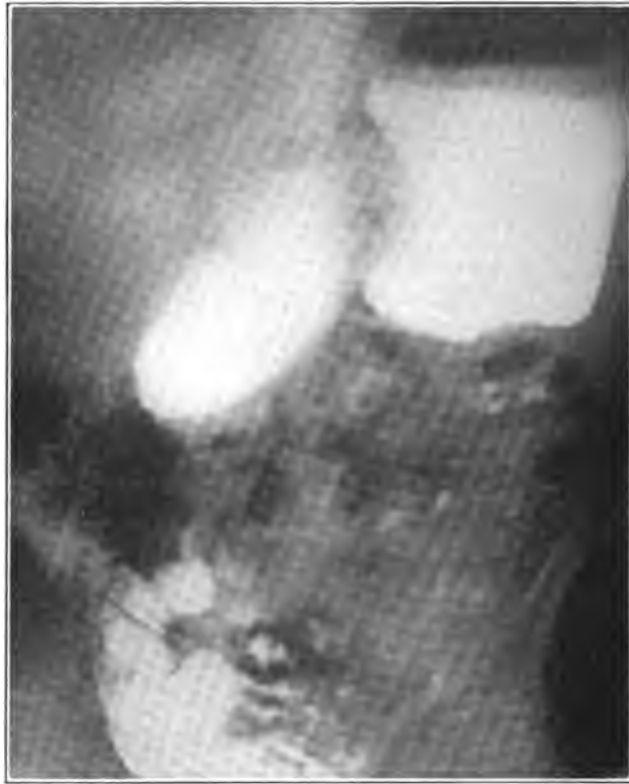
Fig. 71.—Spastic hour-glass stomach. See Fig. 72.

(2) intrinsic spasm set up by a gastric lesion, or (3) spasm associated with abnormal conditions outside the stomach.

This is best carried out by a process of exclusion, for while a parallel tabulation of the traits of these three conditions shows some discouraging similarities, there are, nevertheless, certain practical tests by which differentiation can be effected in most instances.

1. Deformity of the gastric outline produced by an organic lesion is

constant in situation, and unvarying in aspect. If due to a

h and accessible to manipulation, it will sometimes correspond

ible mass. Its borders are sometimes sharp, but more often

shaded off. The niche and accessory pocket of gastric ulcer

gnomonic of themselves. Adhesions about the stomach, other

se from ulcer and gallbladder disease, are relatively rare. If

Same case as shown in Fig. 71. Note disappearance of spasm after administration of belladonna.

stric lumen near the pylorus is markedly encroached on by an

process, some degree of obstruction will be shown by a six-hour

on.

gularity of contour is still seen at repeated examinations. It

be made to disappear by giving an antispasmodic.

Spasm resulting directly from an ulcer or cancer in the stomach

is manifest usually in the segment involved, and especially in the area opposite the lesion. It is constant in situation. It is persistent and unvarying, although it has been claimed that shallow erosions may cause intermittent spasm. If the spasm takes the form of an incisura or hourglass, its borders are clear cut, but if a large area is involved, it may show as an indefinite zone of incomplete filling. The lesion provoking the spasm may be seen as a niche, accessory pocket, or a neoplastic filling defect. The progress of the meal may or may not be retarded, depending on the extent and situation of the lesion rather than on the spasm.

Intrinsic spasm tends to persist at subsequent examination. It cannot be effaced by giving antispasmodics.

Indirect, remotely caused gastrospasm is often brief in duration or intermittent in its appearance. It may be of the migratory type or show a changing aspect from time to time, though continually present in one situation. No tumor mass corresponding to the defect can be felt ordinarily. The borders of the spastic area are sharply delineated, or if the spasm is shifting during the time of the exposure, the gastric contour may be hazily blurred in outline.

Diffuse extrinsic spasm tends to accelerate gastric motility rather than retard it. If the spasm involves the pyloric sphincter, motility is often retarded, but varies from time to time in the same person, so that a six-hour retention may be noted at one examination but not at another. Very often in such cases, the stomach is quite large, and while there is no six-hour retention, the gastro-enterologist may report an excess of secretion.

Remotely reflected spasm is likely to be absent at a second examination. It disappears after the administration of an antispasmodic to physiologic effect.

Of course, it will be readily understood that these differential features are not absolute and inflexible, and occasionally the examiner may be foiled in a satisfactory analysis of his findings. At any rate, he ought not to omit any method that will eliminate indirect spasm from the field of consideration.

A prime quality of remotely reflexed spasm is its instability, so that a second examination may alone suffice to exclude it. A practical test, on which most roentgenologists rely for the exclusion of reflex spasm, is the administration of belladonna or its alkaloid. Irregularity of contour produced by a new-growth, infiltration, or adhesions of the gastric wall is, of course, not altered by this drug. Likewise, the spasm arising
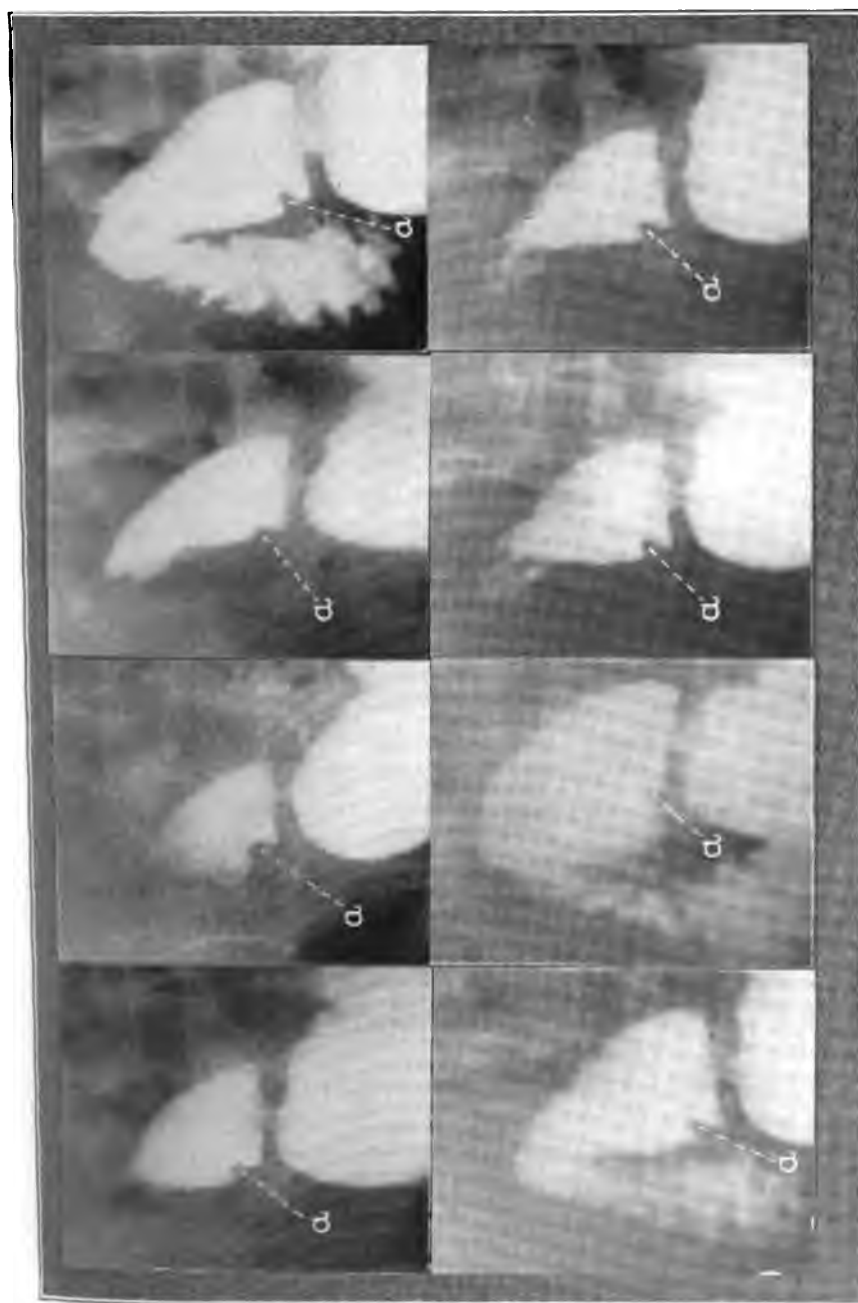
Fig. 78.—Series of bulbus duodeni, showing constant spastic incisura at *a.* Bulb otherwise normal. At operation: Small ulcer, anterior wall of duodenum.

from a lesion, such as the incisura of gastric ulcer, withstands its influence. Spasm reflected from a distant source vanishes.

We have obtained the best results by giving belladonna in the form of the tincture in doses of from 15 to 20 drops three times daily for two or three days, and then reëxamining. The essence of the test, however, does not depend on any arbitrary dose, but on obtaining the physiologic effects of the drug, as shown by dryness of the throat, dilatation of the pupils, etc. If these effects are not obtained, the second examination will be inconclusive. Hence the patient should be seen once or twice daily and the dose increased, if necessary. On the other hand, there may be an idiosyncrasy for belladonna, and this should be kept in mind.

Spasm of any sort, whether intrinsic or extrinsic, disappears under general anesthesia. The spasmodic hour-glass stomach, due to an intrinsic cause, and persisting after the administration of belladonna to physiologic effect, is not present at operation because it is relaxed by deep narcosis. Consequently, the surgeon on opening the abdomen and finding no hour-glass may complain that the roentgen diagnosis is incorrect, and conclude that it is needless to look for any trouble in the stomach. But a careful search will usually reveal a lesion, either in the stomach or, exceptionally, in the duodenum.

In this connection I might say that while belladonna usually relaxes gastrospasm arising from extrinsic causes, the incisura and hour-glass contraction of the stomach associated with duodenal ulcer appear to be an exception, for we have seen several instances in which this variety of spasm withstood the belladonna test.

Spasm of the Duodenum

In the duodenum a probable form of intrinsic spasm which has not been emphasized heretofore is that accompanying duodenal ulcer. Deformity of the bulb has been generally attributed to the ulcer or its scar, producing an organic filling defect. This is doubtless true in many instances, but the following phenomena deserve consideration:

1. In those cases in which organic distortion is present, the deformity noted at the roentgen examination often far exceeds the deformity found at operation.

2. Cases are seen occasionally in which the ulcer or its scar as found at operation is small and quite insufficient of itself to produce a recognizable filling defect in the roentgenogram. This fact made us very skeptical for some time of the validity of Cole's sign. However, these cases

do frequently show pronounced irregularity of the bulbar shadow, and this must be due to some cause other than the organic alteration of the bulbar wall.

3. In the above described type, on plates made in the dorsoventral position, the disfigurement is seen on the lateral borders of the bulb, although the ulcer is usually situated on the anterior wall.

4. The bulbar distortion often displays other characteristics of spasm. It is clean-cut in outline, projects deeply into the bulbar lumen, and is wholly comparable to the incisura of a gastric ulcer.

5. That duodenal ulcer, like other ulcers, is an efficient spasm-producing agent is indicated by its association with spasm in the stomach and elsewhere.

From these facts it seems reasonable to conclude that intrinsic spasm plays an important part in the roentgenologic evidence of duodenal ulcers, and that in the absence of spasm no deformity of the bulb would be seen in many instances and the case passed as negative.

Whether or not any of the remote causes which are believed to induce reflex spasm of the stomach may similarly affect the duodenum is uncertain. There is a more or less current view that the duodenal bulb may be distorted by reflex spasm originating in conditions far removed from the duodenum. In theory this would hold good, since extrinsic spasm has been noted in all other parts of the alimentary canal. But, after a careful view of our cases, we are unable to point out a single specific example of duodenal spasm which originated solely from a remote lesion. Occasionally there is difficulty in securing complete filling of the duodenal bulb, which changes its appearance in each view and is never fully distended, but shows no constant localized deformity. Possibly this may be due to extrinsic spasm, but even so we cannot see how it could be distinguished from the numerous instances in which the cap is not filled because of a scant pyloric inflow or rapid duodenal evacuation. Further, . we would expect extrinsic duodenal spasm, if it exists, to imitate, at least occasionally, the constant and definite spasm of duodenal ulcer. This we have never observed, and it would appear that in the presence of an unchanging bulbar distortion one can safely assume that it is due to an intrinsic cause.

THE EFFECT ON THE JEJUNAL MUCOSA OF EXPOSURE TO THE GASTRIC JUICE *

FRANK C. MANN

— — — —

The investigation was made for the purpose of observing the continued effect of gastric juice on an isolated portion of the jejunal mucosa. It was thought that by concentrating the effect it would be possible to determine the part played by the gastric juice in the production of gastrojejunal ulcers.

The operative procedure consisted in functionally resecting a loop of the first part of the jejunum, varying in length from 6 cm. to 12 cm., and implanting it with intact blood-supply into the posterior wall of the stomach in the region of the antrum of the pylorus. The continuity of the intestine was maintained by anastomosis. In some of the experiments silk or linen sutures only were used; in others, catgut was used for the through-and-through sutures. All the operations were done under ether anesthesia. In this manner the portion of the jejunum which is usually next to the stoma in a gastrojejunostomy was placed in the part of the stomach which is almost always bathed with free acid. Furthermore, the condition of the transposed jejunal mucosa differed from that of the mucosa near the stoma of a gastrojejunostomy in that the former was not protected by the other intestinal secretions. Because of this the effect of the acid should have been many times greater on the transposed jejunum.

Dogs operated on in this manner recovered from the operation and maintained excellent health for many months. At various periods thereafter the animals were killed, and after the gross specimens were studied, sections of the transposed jejunum and of the jejunum near the origin of the former were fixed in various solutions for microscopic examination.

The work of previous investigators has touched on certain phases of this problem. Soresi,[1] in a study of plastic operations on the gastro-

intestinal tract, found that the small intestine could be used as a patch to repair defects in the stomach. His work dealt only with the operative phases. Smith[2] transposed or transplanted portions of many of the viscera in order to determine whether metaplasia took place, but the transposition of the jejunum into the stomach was not included in his operations. He transplanted the gallbladder, the urinary bladder, and the uterus successively into each other and into the peritoneum. A transplantation of the ureter into the gallbladder and uterus was also done. From the results of a large series of experiments he found that the epithelial surface of the implanted organ underwent a change in structure. This change occurred when the epithelium of one organ differed in type from that of the other, and was the result of replacement of the epithelium of the implanted tissue by another derived from the receiving organ. The replacement of epithelium depended on the environmental condition. It did not occur in a neutral environment, such as the peritoneal cavity. He found that the implantation of the gallbladder into different viscera, such as the large and small intestines, produced an active proliferation of gallbladder cells, a rearrangement of the crypts, and an early active infiltration of the subepithelial tissue. When transplanted into the stomach, there was a marked hypertrophy of the gallbladder mucosa. Implantation into the large or small intestine of flaps of gastric mucous membrane caused a disappearance of the chief and parietal cells and the development of a different type of cell which resembled a mucus-forming cell of the pylorus.

Harvey[3] studied the changes taking place in the gastric mucosa at the site of the stoma of a gastroduodenostomy and after pyloric obstruction. He did not study the changes occurring on the duodenal side of the stoma. The changes in the gastric mucosa took place within 7 mm. of the suture line. They consisted in a gradual transformation of the body chief cells into mucus-forming cells. This process reached its maximum about three weeks after the operation. After one month a reverse transformation began and the same cells became ferment cells. The process was completed six and one-half months after operation. Cells were found containing both mucus and zymogen.

The results of the investigation here reported are based on 14 experiments. The specimens were obtained after operation as follows: 2 days, 6 days, 13 days, 22 days, 22 days, 51 days, 83 days, 90 days, 112 days, 146 days, 173 days, 282 days, 291 days, and 330 days.

When the dogs were killed within a week after operation, the speci-

mens grossly presented swelling and edema at the suture line, which are
noted in all recent operations on the gastro-intestinal tract. Away from
the suture line the jejunum did not show any changes. The specimens
obtained after complete healing had occurred showed a few gross changes.
These increased progressively to a maximum a few months after opera-
tion, and consisted of: (1) A slight increase in the thickness of both

Fig. 74.—Photograph of transposed jejunum two hundred days after operation. Note the folds of jejunal
mucosa and the small pockets at each end where the jejunum was folded.

mucosa and muscularis; (2) a throwing of the mucosa into folds which
corresponded roughly to the rugæ; and (3) a change of the color of the
mucosa, which became much lighter and was covered with a thick mucoid
substance (Fig. 74).

While the increase in the thickness was definite, it was not very
marked or constant. The earliest date after operation that a specimen

was obtained showing an increase in thickness was fifty-one days. In four specimens showing the most marked increase in thickness measurements of the transposed tissue and normal jejunum were compared. The average total increase in thickness of the transposed jejunum was 0.65 mm.; the muscularis had increased an average of 0.35 mm., and the mucosa 0.3 mm.

Fig 75 —Photograph of transposed jejunum one hundred and seventy-three days after operation. The large indurated ulcer has a non-absorbable suture at its base.

The microscopic picture varied considerably in the different specimens. This variation was not due wholly to difference in time after operation, because specimens obtained at approximately the same time after transposition did not present a uniform appearance. In a few experiments there was an increase in the mucus-producing cells. In some cases these were increased not only in number, but also in size. Some tubules seemed to be composed almost wholly of goblet cells. In a few

of the specimens there was a very active cell proliferation. This appeared to be an exaggeration of the normal cell division occurring in the base of the glands. In some instances there was a decrease, and in a few areas almost total absence, of gland-cells. In these specimens there might also be an infiltration of the subepithelial tissue. The latter changes may have been due to the changes of environment or to a decrease in the blood-supply. In general, the changes were slight and in

Fig. 76.—Photomicrograph of specimen of transposed jejunum obtained two hundred and eighty-one days after operation. The animal had been given olive oil ninety minutes before being killed. The mucosa was fixed in acetic-osmic-bichromate and stained with hematoxylin. Note that the tubules are perfectly normal. There is considerable fat in the cells at the upper part of tubule (× 160).

many cases it was impossible to distinguish between sections of the transposed jejunum and sections from the jejunum at its site of origin.

If the gastric juice is a primary factor in the cause of gastrojejunal ulcers, an isolated jejunal mucosa exposed almost continually to the gastric juice should show a large percentage of ulcers. This was not the case in our series of experiments. Only one specimen of the animals operated on showed ulceration. This was a hard, indurated ulcer near the pyloric end of the transposed mucosa, and examination showed that it had formed around a retained linen suture (Fig. 75). This is in accord with the clinical experience of W. J. Mayo,[4] and the experimental

results of Soresi[5] in regard to ulceration at the stoma of a gastrojejunos-
tomy. The results of these experiments seem to indicate that the
gastric juice does not play a primary part in the formation of gastro-
jejunal ulcers.

Since the microscopic examination showed that the transposed
mucosa for the most part remained anatomically normal, it was desirable
to know whether it was also physiologically normal. It was possible to
use only one functional test. This consisted in estimating comparatively
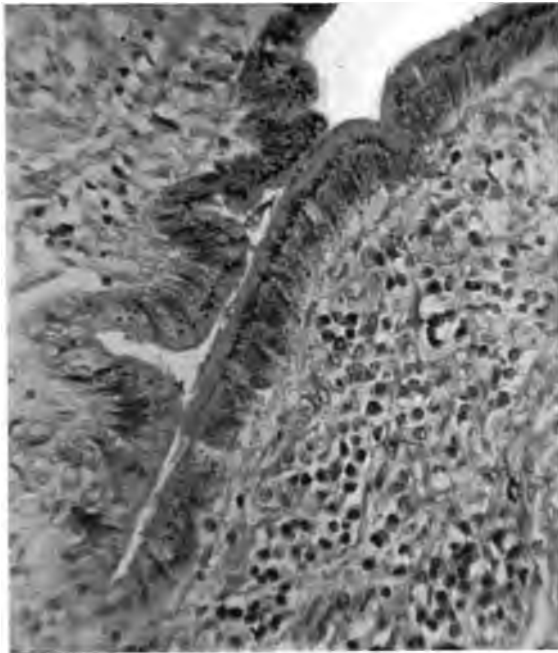
Fig. 77.—Photomicrograph of another tubule from same specimen as Fig. 76, showing fat absorption ($\times$ 220).

the power of the transposed mucosa to absorb fat. In two instances the
animals were given a meal rich in fat, and after ninety and one hundred
and thirty-five minutes respectively they were quickly killed. The
respective lengths of time after operation were two hundred and eighty-
two and two hundred and ninety-one days. A comparison was made of
the fat found in the cells of the transposed mucosa and the upper jejunal
mucosa. Some of the sections were fixed in osmic acid; others in formalin
and stained with Sudan III. The results showed that the power of the

transposed mucosa to absorb fat was but slightly diminished. In many
areas the transposed mucosa showed as large an amount of fat in the
cells as the normal mucosa. Fat was not found uniformly throughout
the transposed mucosa. In some areas it was almost absent. In these
places the cells appeared to be mainly goblet cells. As regards fat ab-
sorption, the transposed mucosa was almost normal.

If more time had been allowed, it is possible that greater changes,
both anatomic and physiologic, might have been observed. However,
the fact that some of the specimens which were secured the longest time
after operation showed very little change validates this possibility. I
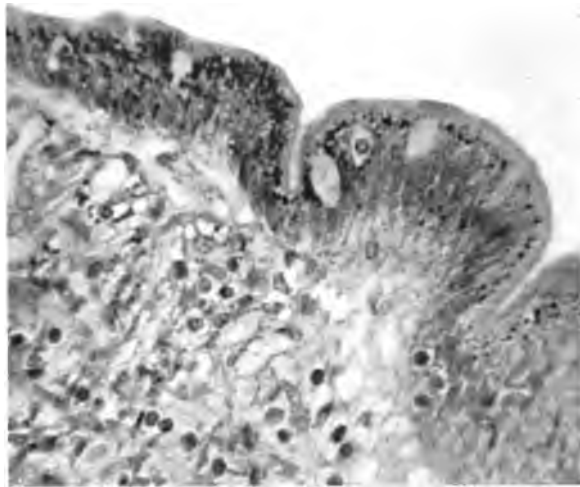
Fig. 78.—Photomicrograph of higher magnification (× 320) of same specimen as shown in Figs. 76 and 77. The
cells are normal and capable of absorbing fat.

believe that the changes which consisted of a loss of gland-cells and sub-
epithelial infiltration were due to a decrease in the blood-supply. After
a while a collateral circulation from the wall of the stomach was estab-
lished, but the capacity of this was not very great, as shown by the injec-
tion of aqueous eosin solution. The constant stretching of the branch
of the mesenteric artery supplying the transposed jejunum decreases its
capacity, so that the blood-supply must be diminished.

SUMMARY

When an isolated portion of the jejunum is transposed into the wall
of the stomach, the following changes may be noted: There may be

slight thickening of both mucosa and muscularis. The mucus-producing cells may be increased in both number and size. There may be an active cell proliferation. In several of the experiments no change in the transposed mucosa was noticed. Ulceration of the mucosa occurred in one experiment, and in this case a non-absorbable suture was found in the base of the ulcer. The gastric juice is probably not the primary cause of gastrojejunal ulcer. The function of the transplant as tested by its power to absorb fat was practically normal.

REFERENCES

1. Soresi, A. L.: "Reconstruction and Repair of Abdominal Organs with Intestinal Grafting," Surg., Gynec. and Obst., 1915, xx, 668–673.
2. Smith, G. M.: "Morphological Changes in Tissues with Change in Environment. Changes in the Gallbladder Following Autoplastic Transplantation into the Gastrointestinal Tract," Jour. Med. Research, 1912–13, xxvii, 399–424.
   "Morphological Changes in Tissue with Changes in Environment. Replacement of Surface Epithelium of Grafted Tissue by Adjacent Epithelium," Jour. Med. Research, 1913, xxviii, 423–440.
   "Morphological Changes in Tissues with Changes in Environment. Gastric Mucous Membrane Implanted into the Intestine," Jour. Med. Research, 1916, xxxiii, 337–344.
3. Harvey, B. C. H.: "A Study of the Structure of the Gastric Glands of the Dog and of the Changes Which They Undergo after Gastro-enterostomy and Occlusion of the Pylorus," Amer. Jour. Anat., 1906–7, vi, 207–243.
4. Mayo, W. J.: "Recurrence of Ulcer of the Duodenum Following Operation," Boston Med. and Surg. Jour., 1914, clxx, 149–151.
5. Soresi, A. L.: "Secondary Ulcers of the Stomach and Jejunum. Formation of Calculi Around Unabsorbable Material Used in Suturing the Intestinal Mucosa," Ann. Surg., 1915, lxi, 328–333.

A FURTHER STUDY OF THE GASTRIC ULCERS FOLLOWING ADRENALECTOMY *

FRANK C. MANN

In a previous study of adrenalectomized animals† the frequent occurrence of acute ulceration of the gastric mucosa and the occasional occurrence of duodenal ulcer were noted. While these ulcers were not found in adrenalectomized animals subjected to continuous etherization, and were infrequent in animals subjected to the removal of only one gland, they occurred in about 90 per cent. of those dying under the characteristic symptoms of adrenal insufficiency after the removal of both glands. The ulcers developed during the moribund period, were apparently peptic, forming at the site of the local hemorrhages in the gastric mucosa, and were true acute ulcers, usually penetrating to the muscularis mucosæ, with a total loss of epithelium. While they occurred in the absence of pancreatic secretion and bile, they appeared to develop only in an acid medium.

In order to determine whether the acid medium was the important factor in the production of the acute ulcers, or whether their cause resided in other factors, such as the special nerve or vascular mechanism of the stomach, the following experiments were performed:

A loop of the first part of the jejunum, varying in length from 6 to 12 cm., was functionally resected under anesthesia and implanted in the posterior wall of the stomach in the region of the antrum pylori. The continuity of the intestine was maintained by an intestinal anastomosis.

Dogs operated on in this manner quickly recovered from the operation and maintained excellent health for many months. Animals killed at various periods after operation demonstrated that the transplanted

mucosa underwent definite changes, but ulcers did not develop except in one instance in which an ulcer was found around a retained silk suture.

In four of these animals, after a considerable length of time had elapsed, the right adrenal was removed, and a few months later the left gland was extirpated. All developed the typical symptoms of adrenal insufficiency and died at various times after the removal of the last gland.

In all these animals definite lesions of the gastric mucosa were found at autopsy. In three there were ulcerations, while in one the mucosa was injected only and showed areas of erosion. In three the jejunal transplant appeared exactly similar to the control. In one there appeared to be a slight loss of jejunal mucosa in pin-point areas, which microscopically proved to be small ulcers.

It was hoped that these experiments would prove clearly whether or not free acidity was the primary cause in the formation of these ulcers. If acidity is the primary cause, the jejunal mucosa, to which an acid medium is foreign, should show the most marked changes. If the primary cause lies in the intrinsic mechanism of the gastric mucosa, the latter alone should be involved.

The results of the experiments show that both factors are of importance. In the three experiments in which the gastric mucosa alone was involved, the transplant having been left intact, the ulcerations and erosions were due either to a primary impairment of the gastric mucosa to which the jejunal mucosa was not subjected, or the acidity developed within the gland tubules and produced its destructive action there first. If the latter is true, the jejunal mucosa might become involved afterward. The experiment in which the transplanted mucosa was involved might be interpreted in this way. The evidence tends to show that the acidity is but a secondary, although necessary, factor and that the primary cause lies in the intrinsic mechanism of the gastric mucosa. However, the fact that changes in the jejunal mucosa occurred in one experiment shows the importance of acidity.

PROTOCOLS

DOG 1.—Under ether anesthesia a jejunal transplant was made on June 29, 1915. The animal quickly recovered from the effects of the operation and its health was excellent. Killed October 19.

Necropsy.—The anastomosis and transplant were in good condition. The transplant showed thickening of the muscularis mucosæ as compared with the control part of the jejunum. The size of the transplant was 7.5

Fig. 79.—Gastric and jejunal mucosa of Dog 1.   This shows the characteristic appearance of the transplant in
normal dogs.

Fig. 80.—Gastric mucosa and transplant of Dog 2.   Note the ulcers in the pyloric mucosa and the normal
appearance of the transplanted jejunal mucosa.

Fig. 81.—Gastric mucosa and transplant of Dog 3. The large ulceration is probably due to a retained silk suture. Note the injection of the gastric mucosa as compared with the jejunal transplant.


Fig. 82.—Gastric mucosa and transplant of Dog 5. Note the marked injection, erosion, and ulceration of the gastric mucosa and the pin-point erosions of the transplanted jejunal mucosa

by 3 cm. The mucosa of the stomach and of the transplant was otherwise negative (Fig. 79).

Dog 2.—Under ether anesthesia a jejunal transplant was made on October 14, 1915. On February 8, 1916, the right adrenal was removed. The condition of the animal was always excellent. On April 11 the left adrenal was removed. The animal died from adrenal insufficiency on April 21.

Necropsy.—The usual findings in animals dying from adrenalectomy were noted. The stomach was contracted and contained about 10 c.c. of bile-stained, acid fluid. The gastric mucosa was injected throughout. In the pyloric region were four ulcers which measured 4 mm. in diameter, and probably extended to the muscularis mucosæ. The transplant was 4 by 2.2 cm., and did not differ in any respect from the controls (Fig. 80).

Dog 3.—Under ether anesthesia a jejunal transplant was made on October 12, 1915. On February 8, 1916, the right adrenal was removed. The condition of the animal was always excellent. On April 16 the left adrenal was removed. The animal died from adrenal insufficiency on April 21.

Necropsy.—The usual findings of adrenalectomized animals were noted. The stomach contained 10 c.c. of bile-stained, acid fluid. The gastric mucosa was bile-stained and injected throughout. In the pyloric mucosa was one small ulcer. At the edge of the transplant in the gastric mucosa a large ulcer was found. The latter, however, may have been partially due to a retained suture. The transplant was 8 by 2.5 cm., and appeared in every respect similar to the controls (Fig. 81).

Dog 4.—Under ether anesthesia a jejunal transplant was made on October 29, 1915. On February 8, 1916, the right adrenal was removed. The condition of the animal was always excellent. On April 16 the left adrenal was removed. The animal died on April 21 from adrenal insufficiency.

Necropsy.—The findings characteristic of an adrenalectomized animal were noted. The stomach contained a small amount of bile-stained, acid fluid. There were no frank gastric ulcers, but the mucosa was markedly injected and there were many areas of erosion. The transplant was 3 by 1.5 cm., and appeared similar to the controls.

Dog 5.—Under ether anesthesia a jejunal transplant was made on October 13, 1915. The animal continued in excellent health. On February 8, 1916, the right adrenal was removed. The animal remained in perfect condition. The left adrenal was removed on April 24. The animal died from adrenal insufficiency on May 2.

Necropsy.—The usual findings in animals dying after adrenalectomy were noted. The stomach contained about 50 c.c. of bile-stained, acid fluid. The fundal mucosa was markedly injected and contained many

ulcers, varying from 0.2 to 0.8 cm. in diameter. The pyloric mucosa showed a few ulcers. In the transplant were a few pitted areas which microscopically proved to be small ulcers. The size of the transplant was 3.5 by 3 cm. (Fig. 82).

SUMMARY

Acute gastric ulcers are found in a large percentage of animals dying from acute adrenal insufficiency. In dogs in which a portion of the jejunum had been transplanted some time previous to the removal of the adrenals the gastric mucosa showed more marked changes than the transplanted jejunal mucosa. This tends to show that the gastric juice as the cause of the ulcer is but a secondary although necessary factor.

SYPHILIS OF THE STOMACH IN ITS ROENTGEN-
OLOGIC ASPECTS *

RUSSELL D. CARMAN

—

A steadily increasing number of case reports evidences a growing
interest in the subject of gastric syphilis. The difficulty of establishing
a diagnosis of this condition beyond cavil, as Eusterman[1] suggests, has
doubtless deterred the publication of many cases in which the proofs,
though reasonably convincing, would not withstand captious criticism.
To substantiate the diagnosis one must rely upon the history, the con-
currence of syphilitic lesions elsewhere, the Wassermann or Noguchi
reaction, the improvement after antiluetic therapy, and the microscopic
examination of gastric tissue. It is quite clear that no one of these is
absolutely decisive unless spirochetes can be demonstrated in the ex-
sected gastric tissue by the microscope. Yet a correlation of all the evi-
dence from all sources may maintain a diagnosis as conclusively as many
other diagnoses which are freely accepted.

From the material published it would appear that there are three
varieties of gastric syphilis: (1) Syphilitic gastritis; (2) syphilitic ulcer;
(3) syphilitic gummas, hyperplasia, sclerosis, and tumor-formation.

The theory that most syphilitics have gastric syphilis, and that in
the eruptive stage they have an eruption in the stomach like that on
the skin, has been quoted by Myer.[2] However, syphilitics may have
gastric symptoms arising only indirectly from their infection; medication
may be responsible for digestive disturbance, and the gastric crises of
tabetics may be mistaken for gastritis, so that the diagnosis of a simple
syphilitic gastritis, without gross tissue changes, is not indisputable.
In any event the condition is not of immediate interest to the roentgen-
ologist, since the x-ray examination would have chiefly a negative value
by its failure to show any organic lesion.

The occurrence of luetic gastric ulcer is well established by case

reports. Neumann[3] claims that 20 per cent. of the round ulcers occur in syphilitic persons. Downes and Le Wald[4] state that gastric syphilis is characterized histologically by the development of gummas, single or multiple, which originate in the submucosa and go on to infiltration, ulceration, and cicatrization in varying degrees. McNeil[5] records an annular syphilitic ulcer almost completely encircling the pylorus. Brugsch and Schneider,[6] in a clinical analysis of over a hundred patients with tertiary lues who had gastric symptoms, found 13 who had signs of gastric ulcer. Cases of ulcer have also been reported by Fenwick,[7] Tuohy,[8] Portis,[9] and Eusterman.[1]

The gummatous, hyperplastic, or infiltrative type of gastric lues is of particular roentgenologic interest because by the x-ray a gumma or extensive thickening of the gastric wall can usually be demonstrated more easily than an ulcer. Notwithstanding the claim that gastric gummas tend to break down before attaining large dimensions, many exceptions have been noted in which the gummas were of large size. Cronin[10] has collected cases from Cornil and others in which gummatous infiltrations were found ranging in diameter from 2 to 24 centimeters. One of Myer's[2] two patients had a tumor the size of half an orange; the other, a tumor as large as a hen's egg. Similar cases in which the tumor-mass was of considerable size have been reported by Meyers,[11] Christie,[12] Muhlmann,[13] Holitsch,[14] Mills,[15] and Morgan.[16] In these cases instructive observations were made with the roentgen ray.

The symptoms alone of gastric syphilis are insufficient to distinguish it from other organic, or even functional, disorders of the stomach. The pain, which is of diverse degrees, is usually referred to the epigastrium, and varies from case to case in its relation to the taking of food. Vomiting occurs in a high percentage of cases. The infrequency of hematemesis in syphilitic gastric ulcer has been pointed out by Fenwick,[7] but some instances of severe hemorrhage have been reported. The gastric analysis most often shows an achylia, and the suggestiveness of this sign has been emphasized by several observers. However, an achylia is more likely to be attributed to gastric cancer, and if, in addition, a tumor-mass is palpable, the diagnosis of cancer will seem most logical.

Although the roentgen signs of gastric lues, whether of the ulcerative or hyperplastic form, are not of themselves distinctive and pathognomonic, they usually furnish decisive evidence of gastric pathology, and, in correlation with the clinical and laboratory findings, give indispensable aid in arriving at a diagnosis. In the ulcerative type the cases

reported by others, as well as those observed in our series, showed hour-glass contraction as their principal sign. Absence of a niche, accessory pocket, or typical incisura—classic signs of simple gastric ulcer—was notable in most cases, the only exception being that recorded by Portis,[9] in which case both an accessory pocket and incisura were present. A casual study of the cases reported suggests that visceral syphilis is char-acterized chiefly by infiltration, and that the gastric ulcers seen are abrasions or shallow erosions of the infiltrated gastric wall; hence their multiplicity and their failure to show a niche. In the hyperplastic type the roentgen signs of a gastric lesion become still more emphatic. The distortion of the gastric outline by filling defects is marked, and this may be associated in various combinations with shrinking of the gastric capacity, stiffening and lessened mobility of the gastric walls, absence of peristalsis, and gaping or obstruction of the pylorus. If the filling defect is associated with a corresponding palpable mass, the whole picture is that of a cancer, and the examiner will at first be inclined to make this diagnosis. However, there are two considerations which may save him from this error: First, notwithstanding the extensive distortion of the stomach, no corresponding mass may be felt and the filling defects are evidently due not to the intrusion of a tumor, but to an infiltration and contraction of the gastric walls. Second, the roentgenologist may be impressed by the discrepancy between the extent of gastric involve-ment and the general condition of the patient, who is often below the cancer age, is anemic rather than cachectic, gives a longer history than that commonly given by cancer patients, *and, on the whole, is not ill in proportion to the extent of disease shown by the x-ray.* In common with other x-ray workers, I have occasionally fancied that there was some-thing in the roentgen appearances of gastric syphilis which helped to distinguish it from cancer, but upon reflection I am convinced that the disproportion between the patient's general condition and the condition of his stomach as revealed by the x-ray was the dominant, perhaps the sole, distinguishing feature, and this, of course, cannot be final and absolute.

Besides cancer and syphilis, there are two other lesions which must be borne in mind; namely, fibromatosis and tuberculosis. Fibromatosis, the "leather-bottle" stomach, which is either benign or malignant, as you prefer to believe, is also characterized by chronicity, and the patients maintain a fairly good physical condition for a long time. The roentgen manifestations of fibromatosis, at least in the cases which I have seen,

were not different from those of an infiltrative gastric syphilis. Tuberculosis of the stomach commonly affects the pyloric end of the stomach, with the production of multiple ulcers and more or less infiltration. Multiple ulcers have been observed also in the ulcerative form of syphilis. While gastric tuberculosis shows definite roentgen evidence of an organic lesion, the character of the process can be predicted only by the exclusion of other lesions.

Obviously, then, an affirmative diagnosis of gastric syphilis requires the earnest coöperation of the clinician and the laboratory worker. As a purely scientific problem, it is beset with doubt and difficulty; as a practical problem, it can often be solved with reasonable certainty by the exercise of reasonable care, and to this every patient is justly entitled. Thus he can sometimes be spared a needless resection of a supposed cancer, or, if operation be necessary, it can be followed up by effective therapy. Among those cases which should be subjected to extraordinarily careful judgment are the cases of gastric ulcer with an achlorhydria, hour-glass stomachs without a niche, markedly contracted stomachs, the cases showing roentgenologic evidence of a gastric lesion which is not typical of either ulcer or cancer, and the cases in which the *x*-ray findings resemble those of cancer, although the patient is under cancer age, and the case as a whole lacks the pronounced characteristics of cancer. In such instances the Wassermann test should not be omitted, and antiluetic therapy should be instituted if the test is positive. This procedure is especially indicated if the gastric lesion is manifestly inoperable. If the lesion is operable, the proof that it is syphilitic should overcome all reasonable doubt, since the patient's right to immediate surgery for a resectable cancer should not be endangered. Thus, on the one hand, the avoidance of a needless operation, and on the other hand, the avoidance of delay of a needed operation, require an abundant exercise of common sense and fair judgment.

From more than a score of cases of gastric syphilis, fairly proved or strongly suspected, which have been under roentgenologic observation in the Mayo Clinic, I have selected the following example:

CASE 141,491.—Woman, aged thirty, married, no children; one miscarriage at seven months. About six years ago, for a period of a year and a half, she was treated for syphilis. For six or eight months past she has been troubled with bloating, vomiting, and epigastric soreness. The condition was aggravated by ordinary food in ordinary quantities, and for some time she has taken "baby-food" only. In six months her

Fig. 85

Fig. 84

Fig. 83

weight has declined from 135 to 84 pounds. Her general appearance does not indicate malignancy. Urine shows a trace of albumin; otherwise negative. Hemoglobin, 80. Gastric analysis: Total acidity, 8, all combined; no food remnants. The Wassermann test on three occasions was strongly positive. First roentgen examination (October 11, 1915): No retention from the six-hour meal. Marked filling defect pyloric por-
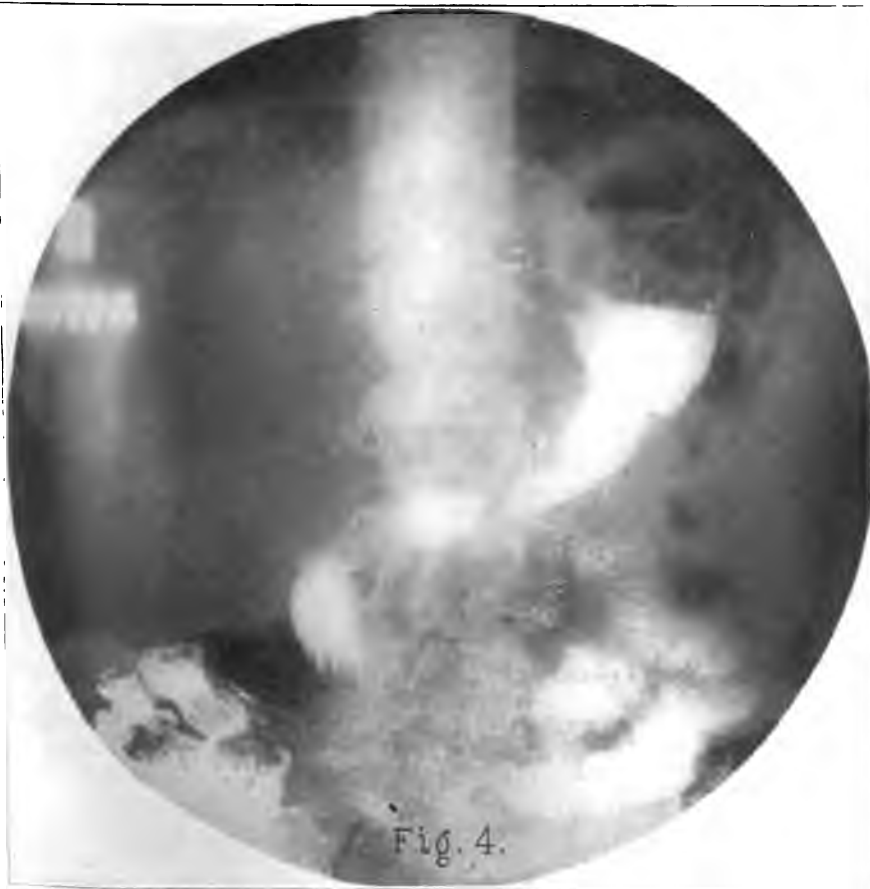
Fig. 86

tion; no corresponding palpable mass. Gastric capacity reduced. Pylorus gaping (Fig. 83). Diagnosis: Syphilis or cancer of the stomach. (Syphilis was thought of first because a filling defect of this size and in this situation, if due to cancer, would give rise to a palpable mass and probably to a six-hour retention.)

From all the findings a correlated diagnosis of gastric syphilis was

made, and the patient was placed on antiluetic treatment, including salvarsan, mercury, and iodids.   The results of treatment are strikingly
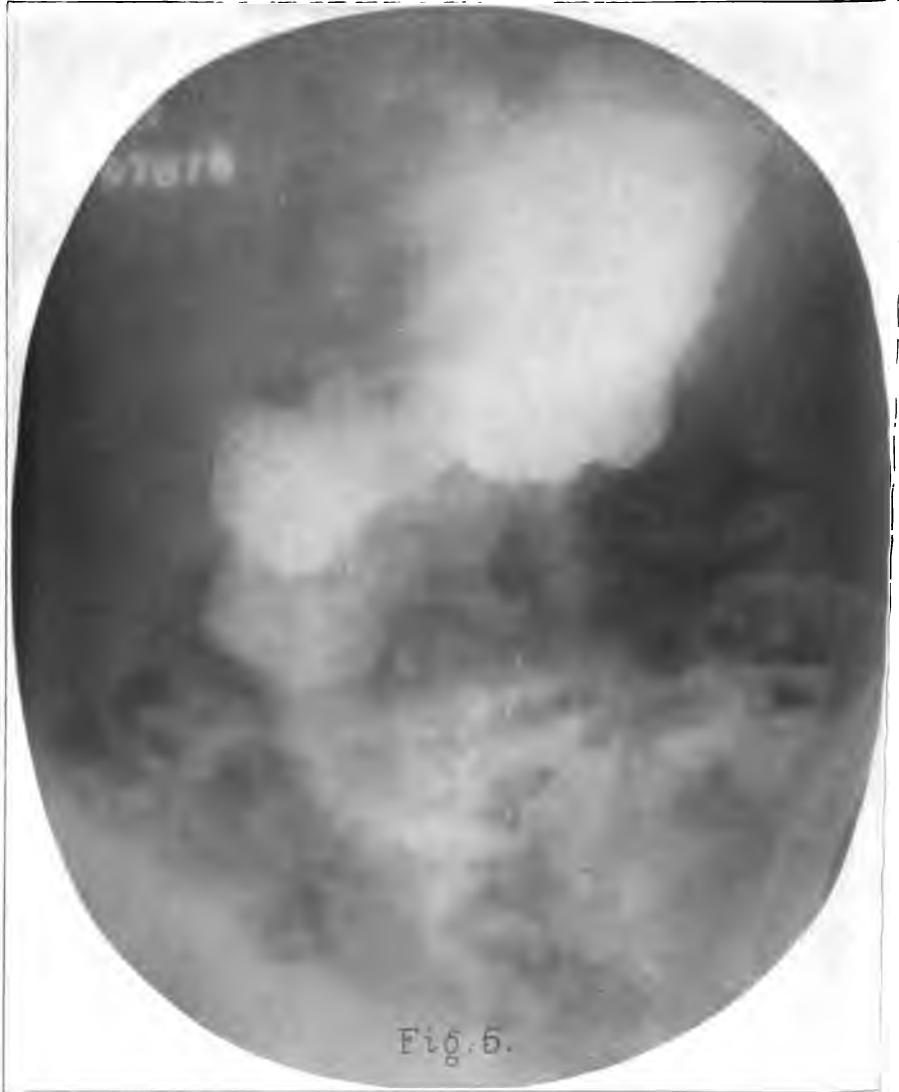
Fig. 87

apparent in the subsequent roentgenograms, and the improvement in the roentgenologic appearance of the stomach was accompanied by a corresponding improvement of the patient's general condition.

Fig. 84 is the roentgenogram taken November 27, 1915. The filling defect has diminished markedly. Fig. 85 is the roentgenogram made October 5, 1916, practically a year after the first examination. It shows a normal stomach with normal peristalsis running all the way to the pyloric ring, and normally flexible gastric walls, as determined by palpation during the screen examination.

Figs. 86 and 87 are the roentgenograms of two other cases of gastric syphilis.

REFERENCES

1. Eusterman, G. B.: "Syphilis of the Stomach: A Clinical and Roentgenologic Study, With a Report of 23 Cases," Amer. Jour. Med. Sci., 1917, cliii, 21–39.
2. Myer, J. S.: "Syphilis of the Stomach, With a Report of Two Cases of Syphilitic Tumors," Interstate Med. Jour., 1912, xix, 974–979.
3. Neumann, I.: "Syphilis." Wien, Hölder, 1896. Form, Vol. 23 of Nothnagel's Specielle Pathologie und Therapie.
4. Downes, W. A., and Le Wald, L. T.: "Syphilis of the Stomach. A Report of Eight Cases with Roentgenologic Findings," Jour. Amer. Med. Assoc., 1915, lxiv, 1824–29.
5. McNeil, H. L.: "Syphilitic Ulcer of the Stomach," Jour. Amer. Med. Assoc., 1915, lxiv, 430.
6. Brugsch, T., and Schneider, E.: "Syphilis und Magensymptome," Berl. klin. Wchnschr., 1915, lii, 601–606.
7. Fenwick, S. and W. S.: Cancer and Other Tumors of the Stomach, London, Churchill, 1902, p. 316.
8. Tuohy, E. L.: "Luetic Contractures of the Stomach. A Report of Two Cases of Hour-glass Stomach with Positive Wassermann Reactions and Improvement under Anti-specific Treatment," Interstate Med. Jour., 1914, xii, 1036–1045.
9. Portis, M. M.: "Syphilis of the Stomach," Medical Clinics of Chicago, 1912, ii, 359–374.
10. Cronin, M. J.: "The Relation of Syphilis to Gastroenterological Diseases," Interstate Med. Jour., 1914, xxi, 1019–1035.
11. Meyers, J.: "Syphilis of the Stomach," Albany Med. Ann., 1912, xxxiii, 563–589.
12. Christie, A. C.: "Studies in Roentgen-ray Diagnosis," Bull. No. 7, War Department, Office of Surgeon General, 1915, p. 22.
13. Muhlmann, E.: "Beiträge zum Schrumpfmagen auf luetischer Basis," Deutsch. med. Wchnschr., xli, 733–734.
14. Holitsch, R.: "Roentgen Findings in a Case of Syphilitic Hour-glass Stomach," Tr. German Roentgen Soc. Congress, 1913, ix, 51.
15. Mills, R. W.: "Points of Value in Roentgenoscopy of the Gastro-intestinal Tract," Jour. Amer. Med. Assoc., 1913, lxi, 1344–1348.
16. Morgan, W. G.: "Syphilis of the Stomach," Amer. Jour. Med. Sci., 1915, cxlix, 392–406.

SYPHILIS OF THE STOMACH: A CLINICAL AND ROENTGENOLOGIC STUDY, WITH A REPORT OF 23 CASES *

GEORGE B. EUSTERMAN

The rarity of syphilis of the stomach is generally conceded, and it is largely on account of its rarity that the disease is of unusual interest. However, from my own observation and that of contemporaries it is safe to say that the condition has a greater incidence than is commonly supposed. Because of a more or less well-grounded skepticism, and because of the possibility of unfavorable criticism, the clinician is constrained to limit his reports to those cases in which the proof of the existence of the disease is most convincing. Objections to clinical diagnosis may be carried so far as to be unscientific. Evidence produced to support the specificity of the lesion in the absence of postmortem examination or microscopic study of resected tissue may be as logical and decisive as many other facts of medicine that are freely accepted.

The earlier literature of gastric syphilis has been thoroughly reviewed by recent contributors to the subject, the survey embracing the histopathologic and gross anatomic descriptions and clinical classifications which constitute the basis of our present knowledge. For convenience, this literature may be divided into three periods, the first extending from the classic report of Chiari[1] in 1891 to the year 1905, the second, from 1905 to 1910, and the third, from 1910 to date. The literature of the first period deals largely with postmortem material. In that of the second period, though a number of cases are reported, the diagnosis rested largely on the history and antispecific treatment. During the third period serology and roentgenology proved useful agents in supplying the data necessary for diagnosis. In 1912, in a comprehensive review, Meyers[2] tabulated 58 cases, among which were included those reported by Birch-Hirschfeld, Fränkel, Dieulafoy, Fournier, Hemmeter, Flexner,

Einhorn, Hayem, Rudnitzki, and others. More recent articles dealing with the subject, and giving case reports, are those of Holitsch,[3] Mills,[4] McNeil,[5] Myer,[6] Morgan,[7] Tuohy,[8] Cronin,[9] Brunner,[10] Lensman,[11] Downes and Le Wald,[12] Brugsch and Schneider,[13] Hausmann,[14] Mühlmann,[15] Smithies,[16] and Niles.[17] To date, our own observations have included 23 cases, a number which seems sufficiently large to warrant certain conclusions.

Symptoms and Diagnosis of Gastric Syphilis

Syphilis of the stomach, as a rule, is a late manifestation of the disease both in the congenital and the acquired form, although in the former it may be present early in life. Briefly stated, the gross lesions are concerned chiefly with: (1) The gumma in its various forms, and (2) diffuse syphilitic infiltration. It is generally conceded that the clinical picture as such may be much like that of non-specific gastric disease, but that usually the results obtained from therapy in the two conditions are different. Many clinicians suspect lues as the etiologic factor in cases of atypical gastric disturbances that do not respond to ordinary dietetic and medical management, a suspicion very frequently justified. Heretofore no characteristic syndrome has been noted or suggested, largely because of lack of sufficient material and doubt as to whether the diagnosis of gastric syphilis was correct. In one instance, a circumscribed lesion, such as a gummatous infiltration of the pylorus, with cicatrization and resulting stenosis, may so closely simulate benign simple ulcer or even carcinomatous ulcer in all its clinical aspects as to defy differentiation. In another, owing to the presence of multiple lesions with their sequelæ or extensive involvement in one and the same organ, the symptoms presented may be so variable as to preclude proper clinical recognition or classification.

The diagnosis of syphilis of the internal organs is based usually on the past history with regard to the initial and secondary symptoms, on the demonstration of late syphilitic manifestations, Wassermann-Noguchi reactions, and the results of specific therapy. In gastro-intestinal cases the Wassermann test is the most helpful means of differentiating syphilitic ulcers, circumscribed or diffuse gummatous deposits, proliferative infiltrations and their sequelæ (cicatrices, ulceration, and fibrous hyperplasia) from simple ulcers and other diseases of the stomach, particularly carcinoma. Often, however, the diagnosis of gastric syphilis is made accidentally. The absence of a history of syphilis, abortion,

sterility, or a negative Wassermann reaction does not exclude the possibility of syphilis. Our own series of cases have taught us this fact plainly. On the other hand, while objective signs of active, latent, or obsolete syphilitic lesions elsewhere (in the bones, glands, skin, nasopharynx, aorta, special sense organs, stigmata) may suggest that the cause underlying the gastric disturbance is specific, such signs are usually absent or not apparent, except in cases of congenital syphilis. Of the greatest importance as indicating gastric syphilis is the combination of anacidity,

Fig. 88.—(108,061.) No retention from the six-hour barium motor meal. Hour-glass stomach. Roentgen diagnosis: Syphilis or ulcer of the stomach. Male, aged thirty-four years. Genital chancre, skin and mucous membrane secondaries twenty years previously. Gonorrhea three times. Gonorrheal arthritis. Chronic urethritis. Moderate alcoholism. Gastric disturbances two years. Cramping epigastric pains promptly after meals. Nausea and vomiting. Appetite fair. Loss of weight, 51 pounds. Liver and spleen palpable. Wassermann 3+. Achylia. Intravenous salvarsan four times. Mercurial inunctions and iodids. Treatment was begun July, 1914. January 5, 1915, symptomatically cured with a gain of 60 pounds. February 2, 1915, Wassermann 3+.

subacidity, or achylia, with a syndrome approximating, but not exactly resembling, that of benign ulcer in some respects, and that of gastric carcinoma in others, and accompanied by roentgenologic findings suggestive mainly of carcinoma. These factors, in addition to a positive Wassermann reaction or a history of infection and other features to be mentioned later, are strong presumptive evidence of gastric lues. However, the fallacy of concluding that a gastric lesion is necessarily luetic if accompanied by a consistently positive Wassermann reaction must

be avoided. The coexistence of syphilis with benign and malignant gastric disease having no obvious etiologic relationship is not uncommon. On that account we have been obliged to discriminate closely in the presence of a positive Wassermann, excluding, as non-syphilitic, cases with a fairly regular syndrome, normal or increased acid values, in which the gross macroscopic appearance at the time of operation or the microscopic picture of the resected tissue was that of the usual chronic cal-

Fig. 80.—(94,691.) No retention from the six-hour meal. Stomach small, showing high hour-glass constriction with marked narrowing and irregularity of the pars media and pars pylorica. Male, aged thirty-seven years. Syphilis nine years previously. Gastric symptoms three years. Epigastric pain promptly after meals, lasting one hour or longer. Continuous complaint with brief periods of remission. Pyrosis, flatulency. Loss of weight, 35 pounds. Appetite good. Wassermann 3+. Hyperplasia of cervical glands, epigastric resistance and tenderness. Total acids 4; no free HCl. Intravenous neosalvarsan, six times. Markedly improved. Gain of 30 pounds.

loused gastric ulcer, and in which the improvement in gastric function was complete or satisfactory without antispecific treatment.

The criticism may be advanced that in making this distinction we have disregarded or overlooked the early uncomplicated syphilitic ulcer or circumscribed gumma, the former of which has been and is still regarded by many as the commonest form of gastric syphilis, and that, therefore, the material herewith presented represents only cases in which the disease was advanced. Such criticism is not justified by the facts to be presented herewith. The most accurate differentiation of early

syphilitic gastric ulcer from non-syphilitic lesions of the stomach can be made only from the study of the symptomatology, gastric chemistry, serodiagnosis, gross pathology, roentgenology, and the results of specific therapy in both. Unfortunately our knowledge bearing on various problems of the subject is still incomplete because the cases reported have not been studied in all these phases. It may be said, however, that
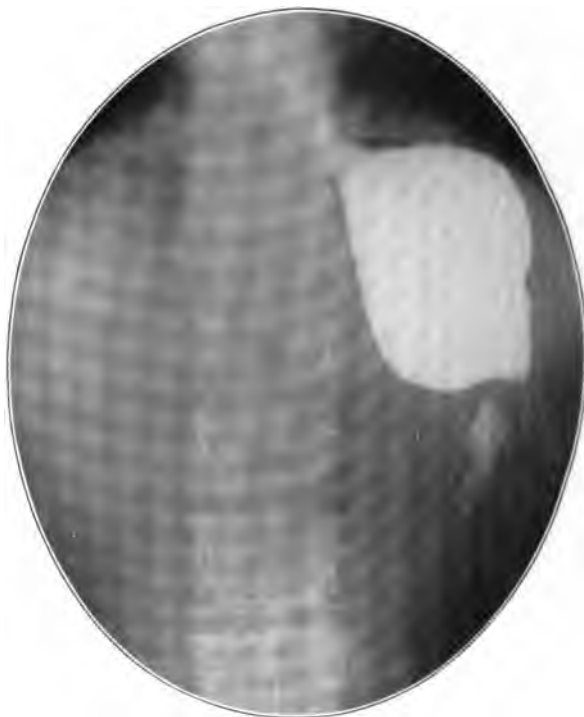

Fig. 90.—(92,014.) Retention of one-fourth the six-hour barium motor meal. High hour-glass con-striction. Reflux of the meal into the esophagus. Male, aged thirty-three years. Syphilis seven years pre-viously. Symptoms three years. Epigastric discomfort due to sense of fullness and heaviness immediately after meals. Generous meal induces pain; emesis necessary for relief. Liquid diet for past two years. Re-cent vomiting of retained food material. Wassermann, total inhibition. Achylia. Salvarsan and mercury caused symptomatic improvement, but moderate pyloric obstruction persisted. Operation advised and ac-cepted.

the rôle played by syphilis in the etiology of gastric ulcer is doubtful because of the following facts: (1) The rarity of cases in which the two are associated—only ⅓ of 1 per cent. in our series of over 2500 opera-tively demonstrated cases of benign gastric and duodenal ulcer; (2) the results of Rosenow's[18] research in regard to the streptococcal origin of gastric and duodenal ulcers; (3) lack of evidence to show that simple

ulcer becomes gummatous in the presence of systemic or gastric syphilis, as stated by Brugsch and Schneider.

In view of our slowly increasing knowledge with respect to the pathology of visceral syphilis in general, and gastric syphilis in particular, there is some reasonable doubt as to the frequency of uncomplicated syphilitic ulcer; moreover, when this type of lesion presents itself, other factors are invariably associated which, in our experience, has not made the specific nature of the lesion difficult to establish in most instances. In accordance with the original view of Klebs, Fränkel, and others we

Fig. 91.—(92,014.) Resected gross specimen. Macroscopically, the resected pyloric portion of the stomach presents a smooth, uniform mucosa with three small superficial erosions. Gross section shows marked thickening of submucosa and muscularis.

recognize as actually specific only those ulcers resulting from the degeneration of a gumma. Such have been reported in considerable number in the literature, yet only one was found in Chiari's postmortem material of 98 cases. There is, however, a considerable difference in the gross pathology of benign and gummatous ulcers that is quite apparent to the experienced surgeon or pathologist on ordinary examination. The latter are invariably multiple, have a predilection for the cardia, the lesser curvature, and especially the pyloric portion of the stomach. Usually they are associated with perigastric adhesions, proliferative

hyperplasia of the gastric walls, and other sequelæ resulting in gastric deformity. To the clinician and roentgenologist these characteristics in conjunction with a markedly altered chemistry rather suggest carcinoma than benign ulcus callosum.

REVIEW OF CASES

The 23 cases that have come under my observation have been either operatively demonstrated or clinically observed and therapeutically managed in the general surgical and medical divisions of the Mayo
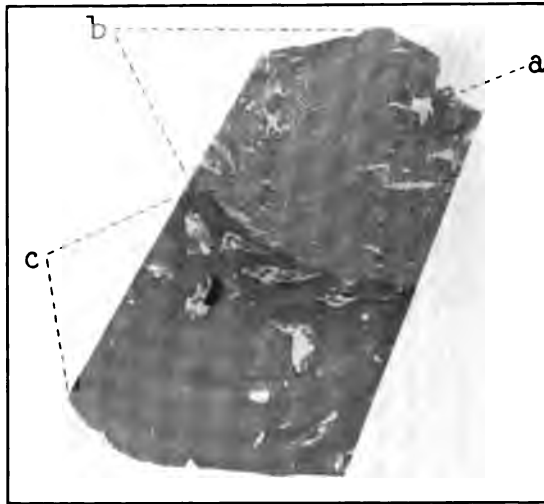

Fig. 92.—(92,014.) Section of tissue from stomach magnified four times. *a*, Atrophic mucosa, curling due to fixing solution; *b*, hypertrophied submucosa; *c*, thickened musculature.

Clinic during the last seven years. With one exception all were of the acquired type of gastric syphilis.

Clinical Consideration.—Sex.—In the 23 cases there were 17 males (74 per cent.) and 6 females (26 per cent.), or about 3 males to each female. This is almost the sex ratio of benign chronic gastric ulcer.

Age.—The youngest patient in the series was twenty, the oldest fifty-seven years. More than two-thirds were below the age of forty. The average age of both males and females was thirty-five. It will be recalled that the average age of the patients having non-malignant ulcers was forty-three years and that of cancerous patients about fifty-four.

Etiology.—The number of patients admitting luetic disease was 13, or a little more than one-half. Twelve (52 per cent.) admitted repeated

gonorrheal infection; in 6 the blood-serum had reacted positively. This appears to be of clinical significance. The number of patients without a history of lues but having positive Wassermann reactions was 9 (40 per cent.). Of the 23 cases, 17 (74 per cent.) showed positive initial Wassermann reactions in the blood-serum. Three of the operatively demonstrated cases in the earliest series antedated the use of the serologic test, but responded definitely to the antispecific treatment. A provocative reaction was obtained in several instances. Of the 6 female patients, all of whom were married, the disease was admitted by 2, and a premarital infection was noted in 2 others. In the case of the remainder
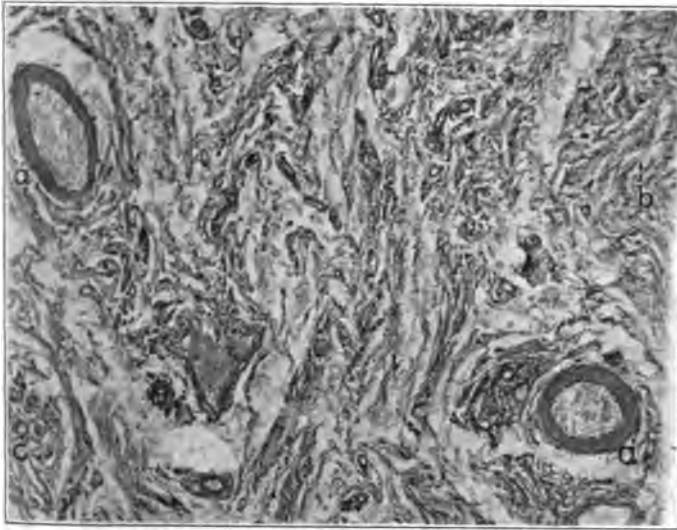

Fig. 98.—(92,014.) Photomicrograph section, magnified 100 times, of tissue from stomach. *a*, Blood-vessels with thickened walls; *b*, dense connective tissue; *c*, nest of phagocytes. No evidence of cancer.

no history was obtainable, and it is most probable that they were infected after marriage. One before marriage had given birth prematurely to a syphilitic fetus. Four reported sterility, single or repeated spontaneous abortions, and tendency to amenorrhea. All were childless except one, and this one had had two miscarriages before the birth of a healthy child. Of the married male group, several reported that their wives had had miscarriages, two had healthy children, and the remainder were apparently sterile.

Time of Onset of Symptoms After Infection.—Definite data bearing on this feature were obtainable in 16 cases. The earliest onset was one

'16—10

year, the latest twenty-eight years, after the disease was contracted. Only 3 gave evidence of the gastric malfunction attributed to the lesion present within the five-year period, 6 between the five- and ten-year period, and 7 between the ten- and twenty-year period. The average was eleven years.

Duration of Symptoms.—The shortest duration of the symptoms on

Fig. 94.—(145,508.) Stomach small, showing high hour-glass. Marked narrowing and irregularity of the pars media and pylorica. Pylorus gaping. No retention. Reflux of the meal into the esophagus. Male, aged twenty-five years. Congenital syphilis. Exploratory operation on stomach three years previously. Gastric disturbances of seven years' duration. Progressive course. Liquid or semisolid foods taken at frequent intervals. Regurgitation. Solid foods cause pain and emesis. Loss of weight, 95 pounds. Numerous stigmata. Filtrate, 50 c.c.; achylia.

admission was seven months, the longest, seven years. Two-thirds fell within the two-year period. The average duration was three plus years. In striking contrast to this is the time-element in the benign ulcer group which so uniformly averages about twelve and one-half years. The significance of such a brief clinical course, in view of the extensive pathologic changes and altered chemistry having such direct diagnostic and prognostic bearing will be referred to later.

Clinical Course.—In 9 cases the course was continuous from the out-set, beginning abruptly with pain and vomiting in 2 instances, definitely intermittent in 4; intermittent, remittent, or irregular in the remainder, but becoming continuous in the latter group after an average of ten months. A distinctly progressive course was characteristic in 20 cases (90 per cent.).

Significance of Clinical Symptoms.—Pain.—Almost invariably the pain was described as situated in the epigastrium or pit of the stomach;

Fig. 95.—(58,949.) Two views: First examination, May 22, 1914. Roentgen examination negative. Female, aged twenty-seven years. Syphilis not admitted. Later it was learned that the husband was being treated for lues. Two miscarriages, one apparently healthy child. Gastric symptoms present one and one-half years. Dull, heavy epigastric distress immediately after meals, lasting ten to fifteen minutes. Two or three hours later, intermittent, sharp epigastric pains radiating through to back. Quantitative food distress. Occasional emesis; flatulency, anorexia, weakness, costiveness, loss of weight. No hemorrhages. Hyperplasia of cervical glands, degenerating gummas in the region of the fifth right costochondral and right sternoclavicular articulations. Total inhibition of hemolysis.

in 1 instance, however, it was felt in the left hypochondrium. Dorsal radiation was noted 4 times. In 9 instances (39 per cent.) the pain was characterized as a distress; in 6 (26 per cent.) as cramping or severe; and in the remainder as dull or gnawing. In three-fourths of the cases the pain ensued immediately after eating and its duration was variable. In 4 cases it was continuous and made worse by alimentation. Definite nocturnal pain was evident in 3 cases only. In the uncomplicated gummatous ulcer type, the pain features simulated those of benign ulcer,

being intermittent, rather periodic and delayed in appearance after meals from one to three hours. It differed from benign gastric ulcer in that anacidity was present and the pain was either only slightly relieved or not relieved at all by food or alkalis. The scirrhus or infiltrated types were associated with pain immediately after eating, which continued until the stomach had emptied itself. Such patients, to avoid discomfort, ate semisolid or liquid foods frequently and in small amounts.

Fig. 96.— (58,949.) Second examination August 31, 1914. No retention from the six-hour meal. Pylorus gaping. Narrowing of the pars media and cardiaca. Roentgen diagnosis: Lesion of the stomach. Achylia. Wassermann persistently positive after repeated intravenous injections of salvarsan, but there was marked general improvement by November, 1915.

Nausea.—Noted definitely in only 3 instances: transient in cases with retarded motility or stenosis or associated with acute seizures.

Vomiting.—This second most important symptom was noted in 19 cases (83 per cent.), and in 10 was present from the outset. In 4 cases retained gastric contents were vomited, although in lesser amount than in cases of benign obstruction.

Hematemesis and Melena.—Recorded in only 1 instance: single hemorrhage by mouth of 1 liter of blood. In fairly authentic cases reported in the literature, however, severe and even fatal hemorrhages have occurred.

Flatulency.—Definite complaint in 65 per cent., and present mainly for a period of one hour after taking food.

Bowel Function.—Marked constipation in 50 per cent.; moderate to normal in 30 per cent. Constipation alternating with diarrheal movements in the remainder, but the former predominating.
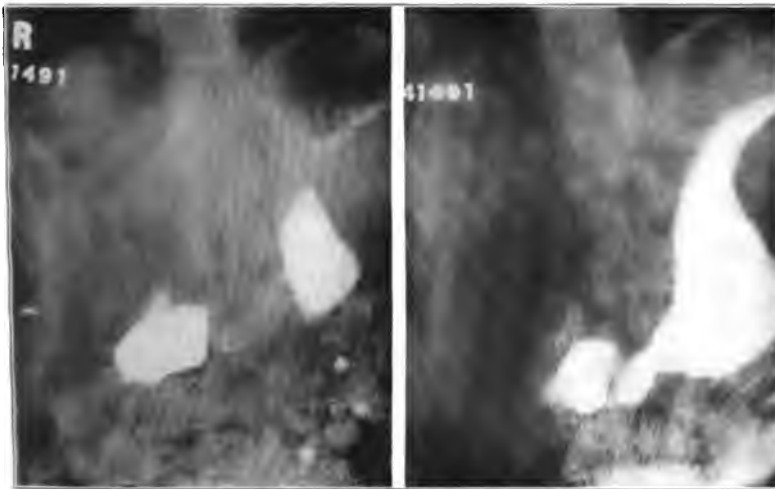
Fig. 97   Fig. 98

Fig. 97.—(141,491.) Two views: September 11, 1915. No retention from the six-hour barium motor meal. Filling defect pyloric end of stomach with no corresponding palpable mass. Female, aged thirty years. Married three years previously. Formerly a London barmaid. Genital chancre and oral mucous membrane secondaries about ten years previously. Two years later gave premature birth to viable syphilitic child. For one year weekly hypodermics of mercury salicylate and "pills" for two years. Gastric complaint of eight months' duration prior to examination; epigastric discomfort soon after eating (eased by soda), even after partaking of a small meal. Gastric analysis by a local physician at outset showed absence of HCL. The acid prescribed disagreed and was voluntarily discontinued. Daily complaint. Appetite excellent. "I could eat all the time." Fresh fruits and soups seemed to agree. Chronically constipated; becoming worse. Ate small amounts frequently, but loss of weight was progressive; altogether, 46 pounds. For the past month forced to vomit to relieve distress attributed to gas. Every third day regurgitation of small amounts of bitter green fluid. Absence of diarrhea or unusual nocturnal pain (clinical signs of contracted stomach). Good color; hemoglobin, 80 per cent. Epigastric resistance, but no palpable mass. Heart, lungs, etc., objectively negative. Wassermann reaction, total inhibition of hemolysis. Spinal fluid reacted negatively.

Fig. 98.—(141,491.) Second roentgenogram taken November 27, 1915, shows marked improvement. After the seventh intravenous salvarsan injection and a three months' course of mercurial inunctions and potassium iodid the reaction was strongly positive. Repeated gastric analysis showed persistent absence of free HCl; absence of peptic activity (Mettes' method) even after dilution of filtered gastric contents with $\frac{1}{10}$ normal HCl in proportion of 1 to 16. Average total acidity, 9. Symptomatically well after third intravenous salvarsan treatment. Treatment was begun September, 1915. Patient discharged as cured January, 1916. Gain of 35 pounds. Present health (May, 1916) excellent. Further antispecific treatment recommended.

Appetite.—Characterized as good in 60 per cent.; abnormal in 10 per cent. (owing to starvation); complete anorexia or "poor" in 15 per cent.

State of Nutrition.—All the patients showed marked loss in weight, over 50 per cent. having lost between 50 to 75 pounds. However, the degree of cachexia and diminished strength was mild and out of propor-

tion to the loss in weight. This condition is converse to that which usually obtains in gastric malignancy.

Blood Estimation.—Of 14 patients examined, the average hemoglobin percentage was 80; average red count, 4,640,000; average white, 5400.

Results of Abdominal Examination.—Definite tumor or mass was absent in 20 cases (90 per cent.) and present in 1 instance (4 per cent.). In 2 cases (9 per cent.) there was a suggestion of "ridge-feel," and in all muscle resistance with marked or moderate tenderness. Visible peristalsis was absent in the retention cases on brief observation. Several
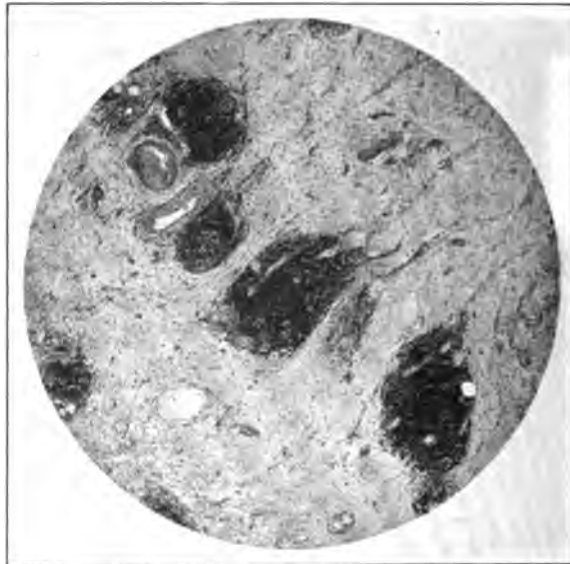
Fig. 99.—(68,261.)   Multiple groups of lymphocytes and marked fibrosis of submucosa.

instances are on record in which palpable epigastric tumor possessing the physical characteristics and mobility of a tumor of the stomach were associated with a history of infection and positive Wassermann reaction. However, our own inability to definitely determine that this tumor had its origin in the stomach, by all the clinical and roentgenologic methods at our disposal, made it necessary to eliminate these from our series, in spite of the fact that such tumors disappeared under salvarsan and other antispecific therapy. Hausmann has pointed out that undoubtedly it has been often erroneously assumed without more definite proof that such tumors were gastric tumors; that gumma of the liver tied off by

cicatrizing contraction, or diffuse syphilitic liver-tissue tied off by cica-
trized gummatous tissue may simulate tumor of the stomach.

Significance of Gastric Analysis.—All the patients, with the exception
of one, who refused the tube, underwent the test. The extract usually
showed poor chymification, especially that of the anacid cases, and was
below normal in amount. The mucus content was not remarkable.

The small amount of gastric extract recovered in most cases was
explained by the pathologic conditions present. The number of patients
with achylia was 18 (82 per cent.) of those examined. Four had an
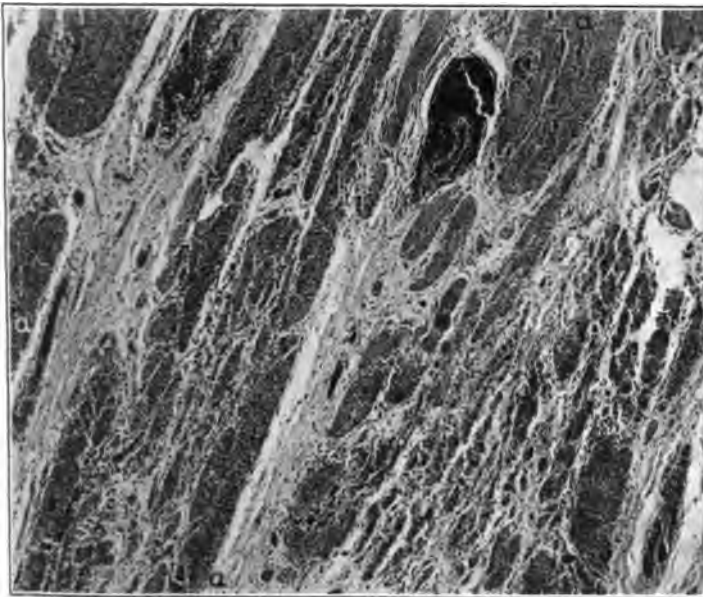
Fig. 100.—(68,261.) *a*, Marked fibrosis of gastric musculature.

average of 22 per cent. free hydrochloric acid; the average total acidity
was 36 per cent. In two of these cases achlorhydria alternated with a
low hydrochloric acid content. Hypersecretion was not noted even in
the retention cases, which numbered 6 (26 per cent.). Blood was found
in the gastric extract in 25 per cent., and occult blood was present in
the feces of 17 per cent. of those examined. Lactic acid and sarcines
were noted in 2 of the retention cases; in one of these Oppler-Boas bacilli
were demonstrated.

A consistent achlorhydria, in fact, achylia, seems almost exclusively
characteristic of luetic gastric disease. Special study has been made of

gastric chemistry in syphilis of the stomach by Barbier, Robin, and others, but to date no definite conclusions have been reached, owing to the variable findings. In the majority of cases in which the diagnosis was verified by postmortem examination or through the study of resected specimens the gastric analyses reported by many competent observers showed absence of free and combined hydrochloric acid. The pathology ranged from circumscribed gummatous ulcers with or without stenosis to diffuse infiltrated and contractured types. On the other hand, fairly convincing
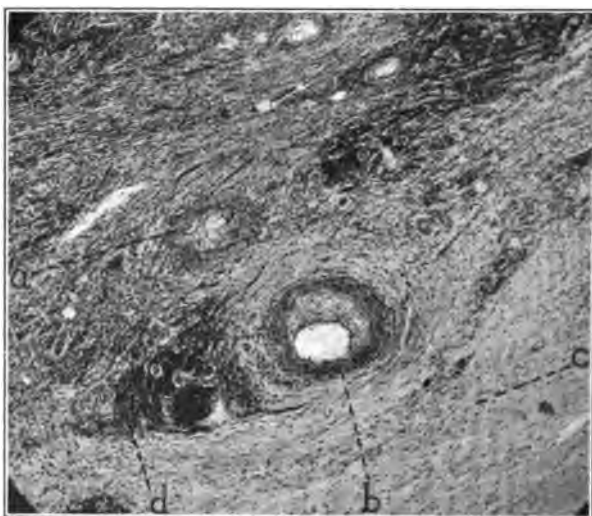

Fig. 101.—(68,261.) a, Obliterated blood-vessel; b, partially obliterated blood-vessel; c, fibrous tissue; d, group of lymphocytes. Male, aged forty-three years. Lues sixteen years' duration. Treated for two years. Gastric symptoms for two years and three months. At the outset, at frequent intervals had "spells" lasting three or four days; left epigastric pain fifteen to twenty minutes after meals, lasting about a half hour. Trouble gradually progressive and daily pain becoming severe; also pyrosis and emesis. Acute pain seizures may last two to six hours. Absence of hyperacidity and stasis. Loss of 20 pounds in weight. Upper abdominal resistance, tenderness in lower left epigastrium, and no palpable mass. Anacidity. Preoperative diagnosis, carcinomatous gastric ulcer. On June 3, 1912, exploratory operation (W. J. Mayo): "Ulceration and thickening (3 x 3¾ cm.) on the posterior wall of the pyloric portion. Remainder of stomach above was small and hypertrophied. Syphilitic appearance." A partial resection was done. Wassermann reaction, after laparotomy, was strongly positive. Antisyphilitic treatment was given, with marked improvement.

case reports by recent contributors to the subject showed the presence of free acid in normal or subnormal amounts. It is reasonable to presume that the extent and the situation of the local involvement and the systemic influence of the syphilitic virus are factors determining the gastric chemistry. However, the preponderance of evidence favors marked reduction of the gastric secretion, either through inhibition of the function of the gastric glands or atrophy of the mucous membrane. This probably has its inception in a gastritis granularis which may be a

manifestation of the secondary or tertiary stage, as the direct or indirect result of the infection. Virchow recognizes an acute syphilitic gastritis which appears in the form of inflammatory infiltration, reddening of the mucous membrane, swelling, etc., and which belongs to the secondary stage. Chiari has described a diffuse and gummatous gastritis as belonging to the congenital form. In gross gastric lesions the more or less diffuse gummatous infiltration of the submucosa which finally extends to the mucosa or the diffuse syphilitic infiltrated type would at an early period affect gastric secretion. An atrophic mucosa was characteristic of all our microscopic sections. Neugebauer recently made a study of the gastric contents of 200 syphilitic recruits. Sixty-two per cent. of them were in the secondary stage, and all showed definite subacidity. In 17 per cent. there was complete absence of hydrochloric acid or mere traces. Brugsch and Schneider, in a review of the gastric chemistry of 100 tertiary syphilitics, conclude that the frequency of achylia in tertiary syphilis in all probability is due to a chronic gastritis, and that a benign gastric ulcer in the presence of systemic tertiary syphilis is associated with diminished secretion of hydrochloric acid. The argument has been advanced that the absence or reduction of the hydrochloric acid and ferments occurs only in advanced cases; that it is due to the rapid emptying of the gastric contents and involvement of the fundic glands, especially in the high contractured or hour-glass types. This explanation does not suffice because the same findings are present in early uncomplicated cases. Moreover, the results of my observations on acid values in benign and even malignant hour-glass stomachs, in which similar mechanical conditions surely obtain, would further seem to controvert such assumption.[19] Hausmann, who has made a critical study of 5 cases under his personal observation, regards anacidity as characteristic of syphilis. After reviewing 135 cases reported in the literature, he feels justified in considering as doubtful those cases with normal or increased secretion, and especially those incompletely studied. Patella,[20] in a review of the 140 cases of gastric syphilis he has found on record, states that the chemistry of gastric secretion was studied in only 11; in 9 of these there was anacidity, and achylia was noted in the cases especially examined. Clark,[21] in one of the more recent contributions to the subject, emphasizes the importance of gastric achylia and absence of free hydrochloric acid.

SIGNIFICANCE OF PATHOLOGY

All the cases showed deformity of variable degree, usually quite marked, with a reduction in size and contour. This was primarily the result of multiple cicatrizing gummatous ulcers or of areas of proliferative infiltration, circumscribed or diffuse, in association with perigastric adhesions. The degree of involvement was invariably in direct ratio to the duration of infection and gastric disturbance. In 4 of the 10 surgically verified cases there was definite hour-glass deformity. One patient had a stricture at the cardia, at the mid portion and at the pylorus. In all the cases the pars pylorica was the most extensively involved, although in 5 instances the involvement extended up both curvatures to the esophageal opening. In addition there was marked thickening and stiffness of the walls. The roentgenograms of two others showed hour-glass contraction, the greater loculus being above. In three instances the ulceration and thickening seemed confined mostly to the posterior wall. In one of these cases the stomach was described as having a ruffled appearance, due to the presence of multiple cicatrizing gummatous ulcers.

Grossly, there is no characteristic which readily enables the clinician to differentiate this form from some types of scirrhous carcinoma, linitis plastica, or sclerotic inflammation secondary to benign ulcer. Sailer[2] has recently called attention to this fact. The final diagnosis often rests with the exploratory laparotomy or the postmortem. However, the latter two forms are quite rare.

Microscopically, the appearance of the tissue is unlike that of benign ulcer or carcinoma. There is usually marked atrophy of the mucous membrane, hypertrophy of the submucosa, and a thickened muscularis owing to a dense connective-tissue infiltration or fibrous hyperplasia. It is quite evident from the microscopic sections that the alteration in structure and function of the gastric mucous membrane is caused partly by a disturbance in the blood-supply. The blood-vessels are invariably obliterated; in addition there is a general contracture of the surrounding tissue, the result of marked fibrosis of the submucosa and muscularis (Figs. 98, 99, 100, and 101). This thickening of the submucosa and muscularis somewhat simulates linitis plastica, but everywhere there is evidence of an obliterative endarteritis and perithelial lymphocytic infiltration which is the most characteristic feature of syphilitic tissue. Although

the spirochetes have been demonstrated in congenital syphilitic tissues, we were unable to find them in these acquired cases.

Gross filling defects, mainly in the lower two-thirds, suggesting extensive disease or involvement, were readily apparent in the other roentgenograms. The congenital case showed a small deformed stomach, the normal portion reduced to a sac at the cardia. To the roentgenologist, the combination of gross filling defect, tendency to hour-glass deformity, absence of palpable mass and six-hour barium residue, and the absence of a proportionate cachexia, suggest gastric syphilis. Technically, however, such findings cannot be differentiated from carcinoma.

The association of syphilitic lesions or their sequelæ in other parts of the body is added proof of the specific nature of the gastric lesion. In this respect, aortitis, aneurysm, and gummas of the liver or hepar lobatum were noted in several instances. Lesions of the skin and mucocutaneous junctures, hyperplasia of the lymph-nodes, tibial periostitis, degenerating gumma of the chest-wall, and late gummatous meningitis, were also present in individual cases. Symmers,[23] in recent postmortem studies of 314 cases of late acquired syphilis, noted the frequency of interstitial orchitis and indurative atrophy of the base of the tongue. Such instances have not been recorded in this series.

RESULTS OF OPERATION AND TREATMENT

Of 10 patients operated on we were unable to get reports from 2. Three (13 per cent.) were cured and 5 (22 per cent.) were much improved. All these patients received antisyphilitic treatment in addition.

Of 13 patients not operated on, reports have been received to date from 12. Two (9 per cent.) are cured, 8 (35 per cent.) are much improved, and 2 are not improved. The total cured and improved number 16 (69 per cent.). This result exceeded expectations and is encouraging. Thorough treatment instituted during the exudative stages gives brilliant results. Advanced cases often require surgical interference because of stenosis or hour-glass deformity, the result of cicatrization or fibrous hyperplasia. If the involvement is extensive, the result of even combined surgical and specific treatment may be disappointing. The desideratum is early diagnosis and intensive treatment.

SUMMARY AND CONCLUSIONS

1. Syphilis of the stomach, though rare, is not as infrequent as is generally supposed. The aid of the Wassermann-Noguchi reaction and

roentgen rays are necessary to establish the presence and the specificity of the lesion.

2. Denial of the disease, lack of evidence pointing to a primary lesion, or absence of a positive Wassermann reaction does not exclude the possibility of gastric syphilis.

3. The diagnosis is based on a history of infection, a consistent positive Wassermann reaction, undisputable evidence of a gross gastric lesion, and—excluding cases showing irreparable extensive disease—a permanent cure by purely antisyphilitic measures. The diagnosis is often accidental. The possibility of syphilis should be considered in every atypical case, or in those not responding to ordinary methods of medical management.

4. The symptomatology which is fairly characteristic of gastric syphilis in view of the cases reported herewith, is suggestive of benign gastric ulcer; the gastric chemistry and roentgen findings rather suggest carcinoma. The average age of patients with acquired syphilis of the stomach is about thirty-five; the duration of the complaint averages three years. In most instances the condition is characterized by an initial intermittent course, followed soon by continuous symptoms and associated with epigastric pain of variable degree, felt shortly after taking food and not relieved by food or alkalis. From the outset there is a tendency toward emesis, a variable degree of flatulency, good appetite, infrequency of hemorrhage and palpable tumor, diffuse abdominal resistance, a progressive course, and marked loss in weight without cachexia.

5. Anacidity or achylia is characteristic of the majority, if not of all, cases of actual gastric syphilis. This can be explained by the influence of the pathologic process upon the gastric mucous membrane.

6. Extensive gastric involvement is frequently present at the time when gastric disturbance first becomes manifest.

7. A gummatous ulcer, usually multiple, and especially a diffuse syphilitic infiltration with a variable degree of contracture (fibrous hyperplasia), thickening, deformity, and perigastric adhesions chiefly involving the pyloric segment, is the usual pathologic condition. Demonstration of the presence of Spirochæta pallida in the resected tissue would be final proof of specificity.

8. Results from antispecific treatment are encouraging in all but very advanced cases. Surgical interference is indicated in certain cases.

Early diagnosis and intensive treatment invariably result in symptomatic cure and structural improvement.

REFERENCES

1. Chiari, H.: "Ueber Magensyphilis," Internat. Beitr. z. wissensch. Med., Festschr. R. Virchow, 1891, ii, 295–321.
2. Meyers, J.: "Syphilis of the Stomach," Albany Med. Ann., 1912, xxxiii, 563–589.
3. Holitsch, R.: "Roentgen Findings in a Case of Syphilitic Hour-glass Stomach," Tr. German Roentgen Soc. Congress, 1913, ix, 51.
4. Mills, R. W.: "Points of Value in Roentgenoscopy of the Gastro-intestinal Tract," Jour. Amer. Med. Assoc., 1913, lxi, 1344–1348.
5. McNeil, H. L.: "Syphilitic Ulcer of the Stomach," Jour. Amer. Med. Assoc., 1915, lxiv, 430.
6. Myer, J. S.: "Syphilis of the Stomach, with a Report of Two Cases of Syphilitic Tumors," Interstate Med. Jour., 1912, xix, 974–979.
7. Morgan, W. G.: "Syphilis of the Stomach," Amer. Jour. Med. Sc., 1915, cxlix, 392–406.
8. Tuohy, E. L.: "Luetic Contractures of the Stomach   A Report of Two Cases of Hour-glass Stomach with Positive Wassermann Reactions and Improvement Under Anti-specific Treatment," Interstate Med. Jour., 1914, xxi, 1036–1045.
9. Cronin, M. J.: "The Relation of Syphilis to Gastro-enterological Diseases," Interstate Med. Jour., 1914, xxi, 1019–1026.
10. Brunner, C.: Tuberculose, Aktinomycose, Syphilis des Magen-Darmkanals, Stuttgart, Enke, 1907, pp. 315–332.
11. Lensman, A. P.: "The Syphilitic Origin of Various Gastro-intestinal Affections," Northwest Med., 1915, vii, 248–252.
12. Downes, W. A., and Le Wald, L. T.: "Syphilis of the Stomach. A Report of Eight Cases with Roentgenologic Findings," Jour. Amer. Med. Assoc., 1915, lxiv, 1824–29.
13. Brugsch, T., and Schneider, E.: "Syphilis und Magensymptome," Berl. klin. Wchnschr., 1915, lii, 601–606.
14. Hausmann, T.: "Die syphilitischen Tumoren des Magens und sonstige syphilitische Tumoren des Oberbauchgegend und ihre Diagnostizierbarkeit, mit besonderer Berücksichtigung der mit Hilfe der topographischen Gleit- und Tiefenpalpation erzielten Resultaten," Ergebn. d. inn. Med. und Kinderh., 1911, vii, 279–331.
"Ein Fall von gummösen Magentumor, geheilt durch Salvarsanbehandlung," München. med. Wchnschr., 1911, lviii, 511.
15. Mühlmann, E.: "Beiträge zum Schrumpfmagen auf luetischer Basis," Deutsch. med. Wchnschr., 1915, xli, 733–734.
16. Smithies, F.: "Syphilis of the Stomach. A Clinical Study of Twenty-six Instances of Dyspepsia Associated with Positive Wassermann-Noguchi Reactions," Jour. Amer. Med. Assoc., 1915, lxv, 572–575.
17. Niles, C. M.: "Syphilis of the Stomach," Jour. Amer. Med. Assoc., 1916, lxvi, 564–65.
18. Rosenow, E. C.: "Production of Ulcer of the Stomach by Injection of Streptococci," Jour. Amer. Med. Assoc., 1913, lxi, 1947–1950.
"Newer Bacteriology of Various Infections as Determined by Special Methods," Jour. Amer. Med. Assoc., 1914, lxiii, 903–906.
19. Eusterman, G. B.: "Hour-glass Stomach and Duodenum," Jour. Mich. State Med. Soc., 1914, xii, 417.
20. Patella, V.: "Early Diagnosis of Cancer of the Stomach," Riforma med., 1916, xxxii, 85–112. Abstr. Jour. Amer. Med. Assoc., 1916, lxvi, 1433.
21. Clark, O.: "Contribuicao ao estudo clinico da syphilis do estomago," Brazil-med., 1916, xxx, 89–96. Abstr. Jour. Amer. Med. Assoc., 1916, lxvi, 1665.
22. Sailer, J.: "Linitis plastica," Amer. Jour. Med. Sci., 1916, cli, 321–333.
23. Symmers, D.: "Anatomic Lesions in Late Acquired Syphilis," Jour. Amer. Med. Assoc., 1916, lxvi, 1457–1462.

GASTRIC AND DUODENAL ULCER *

GEORGE B. EUSTERMAN

My conclusions are based on an examination of the clinical records of 383 cases of gastric and duodenal ulcer operatively demonstrated in the Mayo Clinic during the period from June 1, 1915, to June 1, 1916. The various factors and their relative importance, which in our experience contribute to successful diagnosis, will be considered.

The opinion prevails among clinicians and surgeons of the widest experience that the patient's history is of primary importance. There is still good reason for maintaining this opinion. Others disagree in this. ascribing to the history a minor or secondary rôle. Those inclined to the latter view have freely criticized Moynihan's dictum that the diagnosis of duodenal ulcer may be made by correspondence. I freely concede that an extragastric lesion or functional state may engender symptoms so similar to those of ulcer as to deceive even the elect; that occasionally the usual symptoms in ulcer may be lacking; that the presenting symptoms may be those largely the result of complications. However, in our experience, a characteristic syndrome, carefully elicited and interpreted, is present in the large majority of cases. We should next consider the diagnostic data supplied by a study of the secretory and motor function and by the roentgen ray. Gradually the fact has been evolved that the results of routine gastric analysis *per se*, while essential because of their correlative value in most instances, are of secondary diagnostic importance. It is the determination of motor function rather than secretory function that is the primary consideration. The third factor in diagnosis, the roentgenoscopic and serial roentgenographic examination, which, by virtue of rapid development and the high degree of efficiency attained by skilful and conservative roentgenologists, bids fair to share almost equal honors with purely clinical methods of diagnosis. Because

of occasional inherent shortcomings in both methods, our experience daily teaches us that the one is a necessary complement to the other and that the proper correlation of all data invariably makes for prompt and accurate diagnosis.

Before going into a specific consideration of the material studied, it seems opportune to review briefly the etiology, pathogenesis, and symptomatology of ulcer in the light of our present knowledge.

Clinical and experimental research in the etiology and pathogenesis of peptic ulcer has again become active in the past decade. Numerous theories with respect to the former had been advanced in the past, but no one theory was generally accepted. Acute experimental ulcers with a tendency to prompt spontaneous healing were produced in numerous ways. The infection theory to explain the origin of peptic ulcer has been revived. The recent brilliant findings of Rosenow[1] with respect to the rôle of the streptococcus, based on a series of convincing experiments, seem to prove the infectious origin of gastroduodenal ulcers. Certain clinical facts, recognized for some time, have direct bearing on his conclusions. Chronic infection about the teeth, pyorrhea, or blind alveolar abscesses, chronically infected tonsils, or sinuses about the head, are invariably present in ulcer-bearing patients. Aggravation of symptoms in chronic duodenal ulcer occurs during the months when throat and other streptococcal infections are particularly prevalent. Improvement in symptoms has followed on the eradication of infectious foci, usually in or about the teeth, tonsils, and accessory nasal sinuses. Streptococci of a certain grade of virulence, quite irrespective of their original source, are prone to localize in the mucous membrane of the stomach and duodenum of animals following intravenous injection and produce ulcers which resemble those in man, as shown by Rosenow. The frequent coincidence of disease in the appendix, gallbladder, and duodenum or stomach is best explained on the basis of infection. Rosenow's researches, extending to this field in which all three lesions are simultaneously produced by streptococci of certain virulence and tissue affinity, seem conclusive in support of the infectious origin of most ulcers. He has shown the almost constant occurrence of streptococci in the depths of human ulcers.

Bolton's[2] experiments, conducted to determine the factors which may convert an acute ulcer, whatever its cause, into a chronic ulcer, showed in a convincing way the rôle that delayed motility played in combination with the acid of the gastric juice, which acts both as an irritant and

as a necrotic agent. Rosenow also infers that the localization of streptococci in the depths of ulcers and tissues about them is an important factor in preventing the healing of the ulcer.

The actual factors concerned in the production of pain in peptic ulcer have been made a subject of renewed investigation. This is of immediate importance, inasmuch as epigastric distress or pain is the most constant symptom, and a rational understanding of the pain mechanism is essential to diagnosis and treatment. It has generally been taught and believed that the pain was due to direct irritation of the sensory nerve-endings at the base of the ulcer by the free hydrochloric acid or by mechanical means through peristalsis. Thus the corrosion theory gained many adherents, and fairly effective systems of therapeutics on the principle of the control of corrosion by frequent feeding and sufficient alkalization were the result. It is a fundamental clinical fact that the distress or pain of an uncomplicated gastric or duodenal ulcer bears a fairly definite relation to alimentation, being present presumably at the time of maximum free hydrochloric acid concentration in the stomach, and being relieved by any measure which neutralizes or removes this offending hyperacid chyme. Thus the relation of acidity to pain seemed plausible and valid. On the other hand, clinicians and scientific investigators, for reasons clinical, physiologic, and experimental too numerous to be detailed here, felt that there must be another primary factor in the mechanism of pain production which would adequately explain painful phenomena in the absence of hyperacidity, even in achylia, in extragastric conditions, etc. In this respect the work of Hertz,[3] in particular, Carlson,[4] Cannon,[5] Bolton,[6] Kast and Meltzer,[7] Ginsburg,[8] Edelman,[9] Ducchesi,[10] and others, has seemed to prove quite conclusively that intragastric tension, the result of hypertonus, hyperperistalsis, and pylorospasm, however produced, is the immediate cause of pain. In order to reconcile acidity and pain on the ultimate basis of tension, Hertz offers a solution by explaining that excessive acid chyme passed into the duodenum prevents relaxation of the pylorus. Of course, the effect of this acidity will depend on the alkalinity of the duodenal juice. Thus hyperacidity may cause hyperperistalsis, prevent relaxation of the pylorus in a naturally hyperirritable stomach, and intensified gastric tonus results. Pain is accompanied by contractions, and pain in gastric or duodenal ulcer is said not to be felt unless contractions are present.

Painful muscular contractions occur most frequently at the pyloric end of the stomach, and are due to an exaggeration of the normal reflex.

The deeper layers of the gastric walls, especially the muscular layer, contain more afferent nerve-fibers than the mucosa; hence the ulcerated areas, when irritated, cause an exaggeration of the pyloric reflex, often with normal, and more frequently with hyperacid, secretion. As a result, the rise in intragastric pressure provokes pain. According to Hertz, the sensation produced by pylorospasm varies from a feeling of fullness to the typical hyperacidity pain relieved by milk, alkalis, etc. We have reason to believe that pylorospasm may cause very acute pain, simulating perforation. Especially in the presence of hyperacidity and hyperperistalsis, pylorospasm frequently occurs in disease of the gallbladder and appendix, and this theory best explains the gastric disturbances or suggestive ulcer symptoms arising in disease of these organs. Pylorospasm has even been demonstrated roentgenographically by Cole[11] to be due to reflexes from the terminal ileum and cecal region. Carman,[12] in like manner, has frequently shown it to occur in gastric ulcers remote from the pylorus. The exaggeration of the pyloric reflex, which is regarded as the basis of late pains, may occur in cases of hyperacidity and hypersecretion with or without ulcer, and in so-called vagotonic persons having the combination of visceroptosis and hyperacidity with late pain and no ulcer.

Symptomatology.—In view of the foregoing facts we can anticipate the symptomatology in the majority of cases of ulcers, and at the same time keep in mind those other conditions which may give rise to a similar train of symptoms. In recent years numerous contributions on the subject have appeared from time to time by representatives of the Mayo Clinic. Our clinical observations now are based on a series of over 2500 operatively demonstrated cases of benign gastric and duodenal ulcer. Both types of lesions have many points in common symptomatically, with some variation in a certain percentage of cases. The majority of the case histories reveal a chronic, periodic, or intermittent progressive course, especially notable in uncomplicated pyloric and duodenal ulcers. The periods of exacerbation alternating with symptom-free intervals are variable in duration, but usually extend over a period of several weeks to as many months. Such "spells" are characterized by a daily repetition of symptoms in which pain or distress bears a definite relation to alimentation, and is controlled or relieved by food, alkalis, lavage, or posture. It is not so much the character, degree, location, or radiation of the pain, but the time of its appearance and means of control or alleviation which are diagnostic. If this relation is constant or fairly regular,

other things being equal, the possibility of ulcer should receive primary consideration. The usual accompaniments of burning, gnawing, hunger, or aching pain are pyrosis, belching, often regurgitation of sour fluid, and a sense of distressing fullness in the epigastrium. In over 75 per cent. of the duodenal ulcers this pain appears on an average of three or four hours after eating; in over half of the gastric ulcers, within one-half to two hours after eating. As a rule, the nearer the ulcer is situated to the pylorus, the later the appearance of pain, and the more remote or higher the ulcer is situated along the lesser curvature of the stomach, the earlier the appearance of the pain.

In the event of hemorrhage, which occurs in an average of 30 per cent. of all the cases, along with the other features mentioned in whole or in part, the diagnosis of ulcer is justifiable in over 95 per cent. of instances.

As has been previously stated, both gastric and duodenal ulcers, clinically speaking, have much in common, inasmuch as they tend to be chronic and intermittent in their manifestations and have the same group of symptoms. But duodenal ulcers have more well-defined symptoms, as the regularity of the case histories daily attests. However, in at least one-fourth of the gastric histories this regularity of the clinical course is quite indistinguishable from the duodenal syndrome. We have found it a working convenience to divide our cases into three main groups: (1) The regular type of duodenal ulcer; (2) the regular gastric type; (3) the irregular ulcer type. The first of these needs no further elucidation. The second or gastric type should be considered because it is in the main the syndrome of chronic gastric ulcer, concerning which there has been so much uncertainty in the past. The onset of pain or distress appears sooner after meals, is briefer in duration, usually disappears before the next meal, or may cease and temporarily reappear during this interval. This pain is often eased by food, though not so clearly or completely as the pain of duodenal ulcer. Fear of food-pain is more often noted. Small amounts of food will give ease when larger amounts may provoke pain; nausea, belching, and emesis are more likely to be present. In cases of uncomplicated gastric ulcer careful diet seems to give more relief than in cases of duodenal ulcer. Exacerbations are likely to be more frequent, although shorter in duration, and more easily follow on fatigue, exposure, or dietary indiscretions. In many instances a definite intrinsic gastric complaint runs through the history, less distinctive than in duodenal ulcer, and there is a lack of assuredness in the diagnosis. However, the combination of pain soon after meals, continuing less

clearly to the next meal, with a tender point and pain radiation to the left epigastrium, and the predominance of hematemesis over melena, is strong presumptive evidence that the lesion is situated on the gastric side of the pylorus. The third or irregular ulcer type has lost the distinctive time of onset of symptoms and their control. This is often the result of complicating factors, such as pyloric stenosis, perigastric adhesions with chronic perforation, hour-glass contracture, or extensive ulceration. This type of history does not run a clear-cut course, chemical distress and food ease being less definite, but in spite of an apparent irregularity the complaint is clearly that of an intrinsic gastric lesion. Day by day during the period of attack the pain, vomiting, distress, gas, or regurgitation is the result of taking food. Relief is found in abstinence, bland diet, alkalis, lavage, or other individual agency. In its very inception such a complaint may be irregular and complicated, but in many instances careful inquiry into the earlier period brings out clear-cut ulcer features which strengthen the final diagnosis. Ulcers well up along the lesser curvature may present this irregular train of symptoms. Duodenal and pyloric lesions less frequently present them, and then only when some complicating factor has been superimposed. Such irregularity is sometimes characterized by brief painful seizures simulating hepatic colic, the result of chronic or subacute perforation or unusually painful pylorospasm. The acute perforative ulcers can be recognized by the manifestly severe and grave symptoms. Their proper interpretation is made easier if clinical evidences of ulcer antedated the perforation. However, even skilful clinicians and surgeons erroneously interpret the supervening phenomena (peritonitis and gravitation of fluids to the right fossa, with local muscular rigidity) as an acute perforative appendicitis unless careful inquiry is made. Such inquiry is justified in the face of greatest urgency.

The so-called "silent" or latent nature of ulcer is often strikingly evident clinically, and substantiated by the disclosures of the operating room or postmortem findings. The first tangible signs of an ulcer may be the result of pyloric stenosis, a hemorrhage, perforation, or malignant process. In an average of 5 per cent. of our cases recurring hemorrhage with few or none of the usual associated signs is the primary symptom.

Problems in differential diagnosis are concerned chiefly with instances of disturbed gastric function, the result of extragastric disease. I refer particularly to disease conditions of the gallbladder, appendix, and pancreas—the accessory digestive tract. In many instances such dis-

turbances may simulate disturbances accompanying peptic ulcer even to hemorrhage, so that differential diagnosis is exceedingly difficult, taxing all our resources. Sometimes a proper conclusion is not reached even after extended observation and proper therapeutic management. Generally speaking, careful analysis of symptoms during the period of attack is most vital and helpful. The day-by-day symptoms vary—today one effect, tomorrow another; one day food may ease or relieve, another day it provokes. There is a certain capriciousness, as a rule, not consistent with the usual factors that obtain in the presence of a peptic ulcer. The irregularity is concerned chiefly with the time of the appearance of pain and the influence of food. Probably the basis for this lies in the fact that the stomach functionates normally unless irritated by the contiguous lesion, and the extrinsic lesion is irregular in its influence. Moreover, the periods of exacerbation are less regular in appearance, briefer in duration, except in cases of impacted gall-stones. Usually on one or more occasions during the life history of the disease definite localizing symptoms are present which should be inquired into.

Another factor of great diagnostic, therapeutic, and surgical import is the coexistence of disease in the stomach or duodenum, gallbladder, and appendix. In a recent article I noted the association of chronic cholecystitis or cholelithiasis, or both, and chronic appendicitis in conjunction with peptic ulcer in 9.7 per cent. and 40 per cent. respectively.[13]

THE SIGNIFICANCE OF PHYSICAL EXAMINATION

Of primary importance in the routine examination is the detection of muscle-spasm or resistance, tender point, mass, succussion splash, visible peristalsis, and percussion boundaries of the stomach. A rigid rectus is indicative of an inflammatory or perforative process. Tender point in uncomplicated ulcer, except during some instances of acute exacerbation, is usually absent. There is more or less epigastric sensitiveness in all cases having gastric disturbances irrespective of the cause, so that especial care is necessary in making a proper interpretation. However, a definite localized and fairly constant tender point, often corresponding to the pain area, has diagnostic significance. Chronic or subacute perforating ulcers are invariably sensitive to pressure. Ninety-five per cent. of all epigastric tumors or masses in association with intrinsic gastric symptoms are malignant; the remainder are the result usually of an inflammatory process. A small, non-sensitive, movable mass having a tendency to disappear and reappear is characteristic of a

palpable pylorus. Peristaltic unrest of the stomach signifies obstruction, and is always looked for when evidence of retention is at hand. This sign may often be brought out by careful kneading of the abdomen or by gaseous distention (sodium bicarbonate and tartaric acid). In the large majority of cases the physical examination of the abdomen in benign lesions is of least diagnostic value, owing to the usual absence of signs.

SIGNIFICANCE OF GASTRIC ANALYSIS

Examination of the gastric contents is done routinely unless there are urgent contra-indications. The gastric contents are removed twelve hours after a modified Riegel meal and one hour after an ordinary Ewald test-meal. The recovery of gross food remnants usually signifies organic obstruction. Marked hypersecretion of 200 c.c. or more, in the absence of food remnants, is characteristic of ulcer, other things being equal, and is most frequently found in the presence of pyloric or duodenal ulcers. Hyperacidity is the rule in 60 per cent. of gastric and 75 per cent. of duodenal ulcers. Achlorhydria, except in very old patients, argues against benign ulcer. The presence of blood, fresh or altered, is of relative diagnostic value only. If blood persists on frequent examinations, the possibility of cancer must be considered. Sarcines signify stasis. Normal or subnormal acid values are found in the presence of ulcer in 15 to 20 per cent. of all cases. Hyperacidity and hypersecretion, even stasis of the first degree, are frequently associated with functional states —ptosis and extragastric lesions. In the main, conclusions must not be drawn from a single or even repeated gastric analysis. The real importance of chemical and microscopic analysis of gastric contents is in its correlation with other data. Examination of the feces for occult blood is not routinely done in view of other more direct reliable methods of diagnosis. The nature of a benign callous ulcer invariably precludes a bleeding element; at best the bleeding is intermittent. On the other hand, positive occult blood reactions may be the result of minute hemorrhage extrinsic to the stomach or duodenum, ranging from a bleeding gum to a rectal polyp or internal hemorrhoid. Such examination, however, is uniformly undertaken in certain instances, especially in cases of supposed ulcer associated with anemia, but with no evidence of gross hemorrhage; in cases in which persistent positive reactions may help differentiate between a benign and primary or secondary malignant lesion; and in cases undergoing medical management to determine the influence of treatment.

THE SIGNIFICANCE OF ROENTGENOLOGIC EXAMINATION

The combination of roentgenoscope and roentgenograms, when indicated, marks the most recent important and far-reaching advance in the diagnosis of gastro-intestinal lesions. In the hands of competent experienced roentgenologists this method is sharing honors with the usual clinical diagnostic methods. In their enthusiasm some roentgenologists would do away with all other methods—an attitude both unscientific and harmful in its influence on the profession. If in some instances roentgenologic examinations have usurped usual clinical methods, it was not because the latter were at fault, but because they were not sufficiently employed. Speaking from the standpoint of the internist, the roentgen method has the following particular advantages:

1. The screen gives accurate information regarding form, tonus, peristalsis, size, and position of the organ.

2. The roentgenologic bariumized carbohydrate double-meal method is a most sensitive test for gastric motility, since it shows delay of evacuation beyond six hours and yields information as to hypermotile conditions.

3. The cardinal and most dependable roentgenologic sign of gastric or duodenal ulcer is a defect in the contour of the luminal outline, expressed in terms of niche, accessory pocket (in gastric lesions), or deformity of the duodenal cap. This could be demonstrated conservatively by my associates in studies of large series in an increasingly high percentage of cases.

4. This method affords the only reliable means of localizing the lesion. Although the clinical history and the results of physical and chemical examination invariably justify an unreserved diagnosis of ulcer, they do not indicate with any certainty whether such ulcer is gastric or duodenal. Graham[14] has recently contributed to the literature an exhaustive study bearing on the differential clinical characteristics of both types. He concludes that no symptom or group of symptoms can more than suggest location, and often, as the histories show, the gastric case may have the pure duodenal syndrome, and the duodenal case may quite as clearly give the gastric type of symptoms.

5. The roentgenogram best reveals unexpected instances of multiple ulcers, hour-glass deformity, and other abnormalities, including organic gastric syphilis.

6. The roentgen method has its most unfailing application in the

recognition of gastric cancer, and in the frequent detection of gastric ulcer undergoing malignant change. Besides, it usually gives an index not only as to location in such cases, but also as to type, extent, and operability. Negative roentgen findings in cancer suspects are most convincing evidence of the absence of disease.

While obviously the roentgen examination is essential, it should not be undertaken until a careful history has been elicited and the complete physical and laboratory examination made; it should not be resorted to as a first aid nor should it be contrasted with the clinical evidence, for it is a part of the clinical examination—otherwise erroneous conclusions may be drawn. Daily experience attests the value of the combined procedure in establishing within a brief period the proper diagnosis in all but a negligible few cases.

STATISTICAL REVIEW

During the period between June 1, 1915, and June 1, 1916, there were 275 cases of duodenal ulcer and 108 cases of gastric ulcer operatively demonstrated at the Mayo Clinic, or a total of 383 cases. These are exclusive of the cases clinically diagnosed and placed under medical management.

In the 275 cases of duodenal ulcer the clinical course and characteristic symptoms, or, in other words, the syndrome of duodenal ulcer, was regular in 225 (82 per cent.). The gastric ulcer type of syndrome was present in 8 per cent. The total number of cases with an ulcer syndrome amounted to 90 per cent. In the remaining 10 per cent. the clinical features were atypical, so that in the absence of laboratory data or more extensive observation no diagnostic conclusions could have been reached. Hyperacid gastric contents were noted in 80 per cent., gross pyloric obstruction in 10 per cent., and hemorrhage, single or repeated, in 25 per cent.

A primary clinical diagnosis of duodenal ulcer was made in 81.4 per cent., of gastric ulcer in 4 per cent.—a total of 85 per cent. An erroneous diagnosis of gallbladder disease was made in 9.4 per cent. These percentages average up well with the results of former statistics. Appendicitis was the sole diagnosis in 3.6 per cent. of the cases.

Definite roentgen diagnosis of duodenal ulcer was made in 67 per cent. and the roentgen examination rendered assistance in a further small percentage. In a total of 93 per cent., the diagnosis of ulcer, primary or alternative, was recorded. Of 275 patients, 242 (88 per cent.)

were submitted to the test-meal and roentgen examination. Of 108 patients with chronic benign gastric ulcer, 60 (56 per cent.) had the clinical characteristics of the purely gastric type; 37 per cent. of the case histories, while indicating ulcer quite clearly, did not designate whether it was gastric or duodenal. In the remainder the clinical history was so irregular or insufficient as to have no contributory diagnostic value. Gross obstruction was noted in 14 per cent., hyperacidity of the gastric contents in 72 per cent., anacidity in 2.8 per cent., hemorrhage in 25 per cent.—i. e., hematemesis in 10 per cent., both hematemesis and melena in 12 per cent., and melena alone in 2.8 per cent.

In 86 (80 per cent.) of the 108 cases a primary diagnosis of gastric ulcer was made. The results of the roentgen findings were included in this percentage. In 18 cases (16.6 per cent.) a primary diagnosis of duodenal ulcer was made. Thus there was a primary diagnosis of ulcer in a total of 104 of 108 cases (96 per cent.). This unusual showing and localization of the lesion was made possible through close routine correlation of clinical and roentgen data. Cardinal signs of ulcer were demonstrable in 70 cases (65 per cent.). In another 13 per cent. the roentgen findings of a lesion in correlation with clinical data justified the diagnosis of ulcer. Thus in a total of 78 per cent. of the cases there were direct roentgenologic data, and in this particular series these findings were of primary importance in the diagnosis and localization. Of interest was the presence of a six-hour barium residue in varying amount in 40.7 per cent. of the cases, in contrast to 13.4 per cent. in the duodenal series.

During the same period of one year 1019 cases of gallbladder disease came to operation. Because of the difficulties in making a differential diagnosis in a certain percentage, the cases in which ulcer was considered in the diagnosis were studied to determine what factors gave rise to such diagnosis. In 76—more than 7 per cent.—a primary or alternative diagnosis of ulcer was recorded. Fifty-nine (78 per cent.) were of the chronic cholecystitis or "strawberry" gallbladder type, in which gastric remittent disturbances and, in a considerable measure, characteristic symptoms of ulcer are likely to occur. Gall-stones were present in 17 other cases in which ulcer was considered in the diagnosis—an unusually low percentage (1.6 per cent.), in view of the total number of cases. Taking first the 59 cases of chronic cholecystitis without stones, the following interesting clinical data are noted: In 56 (95 per cent.) pain or distress bore definite relation to the ingestion of food; ease from food was experienced

in 69.5 per cent.; ease from alkalis, in 32 per cent. Duration of attacks at times for periods of two weeks or longer was recorded in more than 55 per cent. Hyperacidity was present in 46 per cent., and hemorrhage in 22 per cent. of the series. Incorrect roentgen diagnosis (ulcer or lesion) was recorded in 22 per cent., and this factor had a large influence in the final diagnosis in view of the clinical symptoms. Food remnants were recorded in one instance only—a six-hour barium residue in two. In numerous instances pylorospasm and direct involvement of the stomach by extensive adhesions were apparent. The hemorrhages are explained on the basis of a follicular erosion of the gastric mucous membrane superinduced by spasm and infection.

In the 17 cases of cholelithiasis similar clinical, chemical, and roentgenologic factors were present to give the basis of a primary diagnosis of ulcer in 59 per cent., and a secondary diagnosis of ulcer in 41 per cent. However, the alternative diagnosis of gall-stones was recorded in all cases because of intervening acute seizures characteristic of hepatic colic. All in all, these data show the extreme difficulty in making satisfactory differential diagnoses under the circumstances in a small percentage of cases.

REFERENCES

1. Rosenow, E. C.: "The Production of Ulcer of the Stomach by Injection of Streptococci," Jour. Amer. Med. Assoc., 1913, lxi, 1947–1950.
2. Bolton, C.: "The Origin of Chronic Ulcer of the Stomach in the Acute Variety of the Disease," Quart. Jour. Med., 1912, v, 429–461.
3. Hertz, A. F.: Sensibility of the Alimentary Tract, London, Frowde, 1911, p. 47.
4. Carlson, A. J.: "Contributions to the Physiology of the Stomach," Amer. Jour. Physiol., 1912–13, xxxi, 151, 175, 212, 318; 1913, xxxii, 245, 369, 389, 398; 1914–15, xxxvi, 153.
5. Cannon, W. B., and Washburn, A. L.: "An Explanation of Hunger," Amer. Jour. Physiol., 1912, xxix, 441–454.
6. Bolton, C.: Ulcer of the Stomach, London, Arnold, 1913, 411 p.
7. Kast, L., and Meltzer, S. J.: "On the Sensibility of Abdominal Organs and the Influence of Injections of Cocaine upon it," Med. Rec., 1906, lxx, 1017–1019.
8. Ginsburg, H., Tumpowsky, I., and Hamburger, W. W.: "Contributions to the Physiology of the Stomach," Jour. Amer. Med. Assoc., 1916, lxvii, 990–994.
9. Edelman: Dissertation (Russian). Abst. in Jahresb. ü. d. Fortschr. d. Physiol., xv, 119.
10. Ducchesi, V.: "Sulle funzione motrici dello stomaco," Arch. p. le sc. med., 1897, xxi, 154.
11. Cole, L. G.: "Relation of Lesions of the Small Intestine to Disorders of the Stomach and Cap as Observed Roentgenologically," Amer. Jour. Med. Sci., 1914, cxlviii, 92–118.
12. Carman, R. D.: "Spasm of the Stomach and Duodenum from a Roentgenologic Viewpoint," Jour. Amer. Med. Assoc., 1916, lxvi, 1283–1287.
13. Eusterman, G. B.: "Essential Factors in the Diagnosis of Chronic Gastric and Duodenal Ulcers," Jour. Amer. Med. Assoc., 1915, lxv, 1500–1502.
14. Graham, C.: "Notes on Gastric and Duodenal Ulcers," Boston Med. and Surg. Jour., 1915, clxxiii, 543–547.

RESULTS OF SURGICAL TREATMENT OF GASTRIC ULCER *

DONALD C. BALFOUR

The surgical treatment of gastric ulcer should not be undertaken with a preconceived idea of the type of operation to be performed. Any routine method of dealing with benign lesions of the stomach is neither intelligent surgery nor a contribution toward further progress in the treatment of diseases of the stomach. Although evidence is conclusive that surgery gives permanent relief in a higher percentage of cases and with less associated risk than any other therapeutic measure, it is also true that the surgical treatment of gastric ulcer may be made still more efficient. Although I am quite aware that other factors than operative technic should be considered, the main purpose of the present paper is to present the result of an investigation to determine the relative merits of the various operative procedures employed in the treatment of gastric ulcer.

The conclusions are based on 677 gastric ulcers operatively demonstrated in the Mayo Clinic during the past ten years. No consideration has been taken of ulcers of doubtful situation. Even "pyloric lesions" in which the ulcer has not been positively located on the gastric side of the pylorus have been excluded, as have been also acutely perforated ulcers and those which, after removal, exhibited evidence of early malignant change.

The impression that the results of operation vary to a large degree with the situation of the ulcer having been confirmed, it was necessary, in order to obtain a fair estimate of results, to classify gastric ulcers into the following groups:

1. Ulcers near the pyloric outlet.
2. Ulcers on the lesser curvature.
3. Ulcers on the posterior wall.

4. Ulcers on the anterior wall.

5. Ulcers producing hour-glass contraction.

Certain principles hold true in the treatment of all gastric ulcers. While the frequency with which gastric carcinoma is preceded by ulcer may be a basis for argument, it must again be emphasized that gastric ulcers do at times become carcinomas. The premise, therefore, that gastric ulcer should, if possible, be excised or destroyed may be accepted as logical. The routine adherence to such a principle, however, is difficult from a technical standpoint, and the absence of positive signs of malignant change may persuade the surgeon, against his better judgment, to base his treatment on the assumption that there is no malignancy. Although fully recognizing the importance of the removal of the ulcer-bearing area because it is a potentially malignant lesion, it should be borne in mind also that malignancy with comparative rarity develops in a gastric ulcer for which gastro-enterostomy alone has been done.

Unfortunately, there is no certain method of consistently determining early malignant invasion of an ulcer. In some instances valuable suggestive evidence is found in the history of the patient, the x-ray findings, and the chemical characteristics of the gastric juice, while in others positive proof is obtained by gland examination. The transitional stage between ulcer and cancer cannot be detected at the operating table, and a segment of the ulcer excised for examination may not demonstrate malignant change, although cancer cells may be present in other portions of the base.

The extent of the induration and the degree of its activity must be taken into careful consideration in arriving at a decision as to the operation of choice. An inflammatory mass of large size, with gross evidences of subacute perforation, as a rule precludes excision or resection, while perigastric extension sufficient to involve other organs, such as the liver or pancreas, should usually be a warning against attempted removal.

1. *Ulcers in the Pyloric Outlet.*—In this group there were 197 ulcers, 29 per cent. of the total. It seems to be indisputable that ulcers close to the pylorus are more readily amenable to successful surgical treatment than those in any other portion of the stomach (Brewer,[1] Woolsey,[2] and others). Particularly when mechanical obstruction has occurred from contraction of the ulcer or by reason of its actual size, operation is followed by eminently satisfactory results. The technical difficulties incident to the removal of such ulcers are less than those encountered with other gastric ulcers, but their surgical treatment demands more mature

judgment as to the correct operative procedure to follow. It is difficult, for example, to determine whether early malignant change has occurred in such ulcers, and inasmuch as usually the pyloric end of the stomach, including the ulcer area, can be resected without prohibitive added risk, considerable responsibility is assumed in deciding that a suspicious lesion at the outlet is not malignant. Conversely, the decision that a lesion is malignant may mean an unnecessary resection. When long-continued obstruction has produced a degree of emaciation which permits of only a gastro-enterostomy, the error of assuming the growth to be malignant may result in an unnecessary pylorectomy later. It is in this type of case also that occasionally a hopeless prognosis is given to the patient, and in which a palliative gastro-enterostomy for the supposed extensive carcinoma is followed not only by relief of symptoms, but by a return to permanent good health.

The relative frequency of operations from January 1, 1906, to November 1, 1916, for gastric ulcers near or involving the pylorus was as follows:

TABLE 1

Posterior gastro-enterostomy	105 (53.0 per cent.)
Pylorectomy (Rodman, Billroth No. 1, Polya, and others)	41 (20.0 per cent.)
Excision and pyloroplasty	12 (6.0 per cent.)
Cautery and gastro-enterostomy	11 (5.5 per cent.)
Anterior gastro-enterostomy	10 (5.0 per cent.)
Pyloroplasty	8 (4.0 per cent.)
Excision and gastro-enterostomy	7 (3.5 per cent.)
Excision	1 (0.5 per cent.)
Reinforcement	1 (0.5 per cent.)
Closure	1 (0.5 per cent.)
Total	197

2. *Ulcers on the Lesser Curvature.*—These comprised 316 of the gastric ulcers, 46.6 per cent. of the total, being thus considerably the most common type, especially in view of the fact that many of the ulcers classified in the preceding group, *i. e.*, ulcers in the pyloric outlet, developed on the lesser curvature. Their tendency to localize on the lesser curvature and to spread onto both anterior and posterior walls of the stomach accounts for the term "saddle ulcer." It has been our experience, however, that such ulcers tend to extend to the posterior wall rather than to the anterior wall. These ulcers frequently illustrate in a marked degree the discrepancy in size between the area of induration and the actual crater of the ulcer. It was in these lesser curvature lesions that the cautery was first employed as a surgical measure. A sufficient number of patients have now been operated on by this method to prove

its safety and efficiency, and our own observations have been confirmed by others, particularly Scudder and Harvey.[3]

Lesions are repeatedly found in which excision would be inadvisable and of decided risk on account of the wide area of induration and of the inaccessibility of the ulcer, due to its high situation on the lesser curvature, but in which complete destruction of the crater of the ulcer can be accomplished with the cautery. For lesser curvature ulcers the following operations were performed:

TABLE 2

Posterior gastro-enterostomy	93 (26.6 per cent.)
Excision	72 (20.6 per cent.)
Cautery and gastro-enterostomy (two years)	62 (17.7 per cent.)
Excision and gastro-enterostomy	37 (10.6 per cent.)
Pylorectomy	20 (5.7 per cent.)
Gastrogastrostomy	14 (4.0 per cent.)
Anterior gastro-enterostomy	11 (3.0 per cent.)
Sleeve resection	10 (2.8 per cent.)
Pyloroplasty	8 (2.0 per cent.)
Cautery and pyloroplasty	7 (2.0 per cent.)
Excision and pyloroplasty	7 (2.0 per cent.)
Jejunostomy	3 (0.8 per cent.)
Exploration	2 (0.5 per cent.)
Suture compression	2 (0.5 per cent.)
Reinforcement	1 (0.2 per cent.)
Total	349

3. *Ulcers on the Posterior Wall.*—There were 63 ulcers on the posterior wall, constituting 9.8 per cent. of the series. These have an added surgical interest, since, with the problem of the local treatment of ulcers, various routes to gain access to the ulcer may be chosen by the surgeon; *e. g.*, through the gastrohepatic omentum, through the mesocolon, by separation of the omentum from the transverse colon (Pauchet[4]), or through the anterior wall of the stomach. If the crater of the ulcer is not of large size, and there is little evidence of peritoneal irritation about the ulcer area, its excision may be attempted. Even if the ulcer has per-

TABLE 3

Posterior gastro-enterostomy	17 (21.0 per cent.)
Pylorectomy	10 (12.5 per cent.)
Excision and gastro-enterostomy	8 (10.0 per cent.)
Gastrogastrostomy	8 (10.0 per cent.)
Pyloroplasty	6 (7.5 per cent.)
Cautery and gastro-enterostomy	6 (7.5 per cent.)
Anterior gastro-enterostomy	5 (6.0 per cent.)
Excision	5 (6.0 per cent.)
Jejunostomy	4 (5.0 per cent.)
Cautery and pyloroplasty	4 (5.0 per cent.)
Excision and pyloroplasty	2 (2.5 per cent.)
Sleeve resection	2 (2.5 per cent.)
Reinforcement	2 (2.5 per cent.)
Closure	1 (1.2 per cent.)
Total	80

forated into the pancreas, it may be still possible and safe to separate the stomach from its resulting attachment, trim out or sterilize the edges of the ulcer, and close the defect. The operations indicated in Table 3 were used in this group.

4. *Ulcers on the Anterior Wall.*—Ulcers on the anterior wall constitute a relatively small group, there being but 17 in the series, 2.5 per cent. of the total. Such ulcers are easily excised by knife or cautery unless perforation has occurred with attachment to the anterior abdominal wall. The following operations were made in this group:

TABLE 4

Excision	6 (25.0 per cent.)
Pylorectomy	5 (20.8 per cent.)
Cautery and gastro-enterostomy	5 (20.8 per cent.)
Pyloroplasty	3 (12.5 per cent.)
Posterior gastro-enterostomy	2 (8.3 per cent.)
Excision and pyloroplasty	2 (8.3 per cent.)
Jejunostomy	1 (4.0 per cent.)
Total	24

5. *Ulcers Producing Hour-glass Contraction.*—In the group of ulcers producing hour-glass contraction are 58 cases, 8.5 per cent. of the total number. The characteristic deformity warrants a separate classification, although the contraction may be produced by an ulcer of the anterior or posterior wall or an ulcer of the lesser curvature. These are most interesting from a surgical standpoint, for they tax the resourcefulness and skill of the surgeon and stimulate his ingenuity.

A wide variety of operative procedures are at the choice of the surgeon, the selection being governed by the condition of the patient, the pathologic findings, and the capability of the surgeon. The ulcer which has produced the deformity may be so situated that resection of a complete segment, including the ulcer and the scar, may be possible. This operation, which entails an end-to-end union of the resected stomach, has given excellent results in our hands, and has been reported upon favorably also by others (Haines).[5] It has been recently shown by Stewart and Barber that, after "sleeve resection," the motility of the stomach more nearly approximates the normal than it does after resection of a V-shaped segment from the lesser curvature.

However, this, or in fact any, type of resection is not always possible, for the ulcer may have become so firmly fixed that the stomach cannot be mobilized, under which circumstances drainage must be procured either by gastrogastrostomy or by gastro-enterostomy on the proximal or distal segment of the stomach. Should the ulcer be situated on the anterior wall, and should the greater part of the scar be accessible, sat-

isfactory results may be obtained from excision of the ulcer or from puncture with the cautery point and correction of the original deformity by a gastroplasty.

The operations which have been done in the Clinic for hour-glass contractions are:

TABLE 5

Gastrogastrostomy	22 (39.0 per cent.)
Posterior gastro-enterostomy	8 (13.8 per cent.)
Pyloroplasty	8 (13.8 per cent.)
Sleeve resection	4 (6.7 per cent.)
Cautery and gastro-enterostomy	4 (6.7 per cent.)
Pylorectomy	4 (6.7 per cent.)
Anterior gastro-enterostomy	2 (3.4 per cent.)
Jejunostomy	2 (3.4 per cent.)
Excision	2 (3.4 per cent.)
Excision and pyloroplasty	2 (3.4 per cent.)
Total	58

In the compilation of these statistics the mortality records detail important information as to the relative risk of the various types of operation, as well as the risk according to the situation of the ulcer.

In Tables 6 and 7, although there are several figures to which I might allude, I would draw attention to the fact that in 87 operations by the cautery method combined with gastro-enterostomy, there was one death. Moreover, in the case of this patient a double operation was done, the primary operation being cholecystectomy for a septic gall-bladder in the subacute stage. The necropsy report stated that the stomach was in perfect condition and that the cause of death was septic cholangitis.

TABLE 6.—A SERIES OF 670 GASTRIC ULCERS ACCORDING TO TYPE OF OPERATION

(JANUARY 1, 1906, TO NOVEMBER 1, 1916)

	OPERATIONS	MORTALITY
Posterior gastro-enterostomy	228	4 (1.7 per cent.)
Cautery and gastro-enterostomy	87	1 (1.1 per cent.)
Excision	84	4 (4.7 per cent.)
Pylorectomy	77	6 (7.7 per cent.)
Excision and gastro-enterostomy	52	2 (3.8 per cent.)
Anterior gastro-enterostomy	27	1 (3.7 per cent.)
Pyloroplasty*	26	2 (7.0 per cent.)
Excision or cautery and pyloroplasty*	35	3 (8.5 per cent.)
Gastrogastrostomy	23	1 (4.3 per cent.)
Sleeve resection	12	0 (0.0 per cent.)
Miscellaneous	10	0 (0.0 per cent.)
Jejunostomy	8	1 (12.5 per cent.)
Total number reported in the series	670	24 (3.5 per cent.)

* This mortality is not representative of pyloroplasty by the Finney method, which in our experience in ordinary cases has given a mortality of less than 3 per cent. The group of cases in which the operation was performed included a number of poor surgical risks, with extensive local disease, so that the operation was often one of expediency rather than one of choice.

TABLE 7.—A SERIES OF 670 GASTRIC ULCERS ACCORDING TO POSITION
(JANUARY 1, 1906, TO NOVEMBER 1, 1916)

	CASES	MORTALITY
Ulcers of the lesser curvature	349 (52.0 per cent.)	12 (3.4 per cent.)
Ulcers close to or involving the pylorus.............	197 (29.0 per cent.)	3 (1.5 per cent.)
Ulcers on posterior wall.....	80 (12.0 per cent.)	6 (7.5 per cent.)
Ulcers on anterior wall	24 (3.5 per cent.)	1 (4.0 per cent.)

In considering the results of the various operations employed in the treatment of gastric ulcer it would be advisable to state the basis on which these results were compiled. The information was obtained through a form letter sent to each of the patients operated on in the Mayo Clinic for gastric ulcer from January 1, 1906, to July 1, 1915. The letter was so constructed that we believe we have obtained an accurate estimate of the result of the operations, for inasmuch as they were performed primarily for the relief of subjective symptoms, the patients become the final arbiters as to the success of the treatment. It has further been our experience that those failing to reply to inquiries of this kind are likely to be enjoying good health. It should be noted that at least a year and a half has elapsed since the last case considered in this report. Criticism may be offered that the present health of the patients operated on as recently as eighteen months ago is not a criterion of the late results, but experience has shown that a recurrence of symptoms rarely develops after the patient has had relief for a year. It is also a fact that in the event of such recurrence it is due probably to the development of a new ulcer rather than to a failure to cure the original ulcer.

The results of operation in all cases of gastric ulcer are tabulated in Table 8.

TABLE 8.—RESULTS OF OPERATIONS FOR GASTRIC ULCERS
(FROM JANUARY 1, 1906, TO JULY 1, 1915)

Total number of patients heard from............	285
Cured.......................................	159 (55.7 per cent.)
Greatly improved...........................	65 (22.8 per cent.)
Slightly improved...........................	28 (9.8 per cent.)
No better...................................	33 (11.5 per cent.)
Satisfactory results...........................	224 (78.9 per cent.)

The percentages are based on information from 285 patients who were operated on previous to July 1, 1915. Deaths which occurred months or years after operation are excluded in this report, but are being carefully investigated and will undoubtedly contribute much desired information as to the life expectancy and the possibility of the development of cancer as well as other fatal late complications in those operated on for gastric ulcer.

TABLE 9.—RECAPITULATION

Operation	Number	Satisfactory Results	Operative Mortality	Secondary Operations
Posterior gastro-enterostomy	228	84 per cent.	1.7 per cent.	1.8 per cent.
Pylorectomy....................	77	90 per cent.	7.1 per cent.	3.9 per cent.
Excision and posterior gastro-enterostomy....................	52	83 per cent.	3.8 per cent.	3.9 per cent.
Cautery and posterior gastro-enterostomy....................	87	*	1.1 per cent.	0.0 per cent.
Excision......................	84	57 per cent.	4.7 per cent.	32.0 per cent.
Sleeve resection.................	12	90 per cent.		
Anterior gastro-enterostomy	27	72 per cent.	3.7 per cent.	3.8 per cent.
Pyloroplasty....................	26	75 per cent.	7.0 per cent.	15.0 per cent.

* So little time has elapsed since this operation was instituted that a statement regarding the present condition of the patients would be of no real value.

TABLE 10.—REPORT ON SECONDARY OPERATIONS ON GASTRIC ULCERS
(47 CASES; 6.8 PER CENT. OF 670)

(FROM JANUARY 1, 1906, TO NOVEMBER 1, 1916)

Original Operation	Time Since First Operation	Cause for Second Operation	Second Operation
Excision, 27 cases	1–1.5 yrs., 7 cases; 2–2.5 yrs., 5 cases; 3–3.5 yrs., 5 cases; 4 yrs., 1 case; 4–10 mos., 4 cases; 1–2 wks., 3 cases; 10–18 days, 2 cases	Obstruction, 10; ulcer bleeding, 3; ulcer, 3; hour-glass, 3; distention, 2; adhesions, 1; subacute perforation, 1	Posterior gastro-enterostomy, 25; anterior gastro-enterostomy, 1. Adhesions were freed in 2 of the above cases. An old scar excised and a transfusion in another
Excision and posterior gastro-enterostomy, 2 cases	2 mos., 1 case; 6 days, 1 case	Obstruction from kinked pylorus, 1; obstruction and abscess, 1	Anterior gastro-enterostomy, 1; drainage of abscess, jejunostomy, and transfusion, 1
Excision and pyloroplasty, 4 cases	2 yrs., 2 cases; 1 yr., 1 case; 1 mo., 1 case	Ulcer, 2; abscess, 1	Cautery and posterior gastro-enterostomy, 1; excision and gastro-enterostomy, 1; posterior gastro-enterostomy, 1; drainage of abscess, 1
Pylorectomy, 3 cases	6 yrs., 1 case; 3 yrs., 1 case; 5 days, 1 case	Jejunal ulcer, 1; carcinoma of stomach, 1; acute obstruction and dilatation, 1	Anterior gastro-enterostomy (Murphy button), 1; transverse colon resection and resection of jejunum and jejunostomy ten days later, 1; exploration, 1
Anterior gastro-enterostomy, 1 case	1 week, 1 case	Bile regurgitation, 1	Entero-anastomosis (Murphy button), 1
Posterior gastro-enterostomy, 4 cases	3 yrs., 1 case; 1 yr., 1 case; 2 wks., 1 case; 10 days, 1 case	Ulcer, 3; ulcer causing hour-glass, 1	Freeing adhesions, 1; enlargement of gastro-enterostomy, 1; excision of ulcer, 1; resection of pylorus, 1
Gastrogastrostomy, 4 cases	3 yrs., 1 case; 2 yrs., 1 case; 1 yr., 1 case; 1 mo., 1 case	Hour-glass, 1; adhesions, 1; bleeding ulcer and adhesions, 1; obstruction, 1	Posterior gastro-enterostomy, 2; anterior gastro-enterostomy, 1; anterior retrocolic gastro-enterostomy and splenectomy, 1
Incision and drainage, 1 case	2 yrs., 1 case	Pyloric obstruction, 1	Posterior gastro-enterostomy, 1
Reinforcement, 1 case	3 yrs., 1 case	Ulcer, 1	Posterior gastro-enterostomy, 1

Table 9 is a recapitulation of the results of the various operations for gastric ulcer, with the operative mortality and the percentage of the patients so operated on who returned for secondary operations.

Table 10 is an abstracted compilation of these secondary operations.

There are certain facts in the above tables which appear to justify emphasis.

1. For ulcers at the pylorus, posterior gastro-enterostomy is the operation of choice in the poor surgical risk, for although pylorectomy is followed by better results, the operative mortality is distinctly higher. The cautery is a useful adjunct in selected cases.

2. For ulcers on the lesser curvature, cautery by the method described in a previous paper[7] and gastro-enterostomy is the operation of choice.

3. Local excision alone of such ulcers is inadequate, 32 per cent. of patients so operated on ultimately requiring further operative treatment; namely, gastro-enterostomy.

4. Sleeve or segmental resection, especially in large high ulcers and hour-glass contraction, in suitable cases is not only a relatively safe operation, but has been followed by good results.

5. The lowest operative mortality in the more common operations was associated with cautery and posterior gastro-enterostomy.

6. Ulcers on the posterior wall are associated with the highest operative risk, while those at the pylorus are of least risk.

REFERENCES

1. Brewer, G. E.: "A Critical Review of a Recent Series of Operations upon the Stomach." Ann. Surg., 1907, xlv, 687–698.
2. Woolsey, G.: "The Surgical Treatment of Gastric and Duodenal Ulcers," Med. Rec., 1916, lxxxix, 592–596.
3. Scudder, C. L., and Harvey, S. C.: "Is the Employment of Actual Cautery in the Treatment of Chronic Ulcer of the Stomach a Safe Procedure?" Surg., Gynec. and Obst., 1916, xxiii, 719–724.
4. Pauchet, V.: "Traitement de l'ulcere chronique de l'estomac," Presse méd., 1916, xxiv, 445–448.
5. Haines, W. D.: Personal communication.
6. Stewart, C. D., and Barber, W. H.: "Segmental Resection for Gastric Ulcer: A Preliminary Report Based upon Clinical and Experimental Studies," Ann. Surg., 1916, lxiv, 527–536.
7. Balfour, D. C.: "The Treatment by Cautery of Gastric Ulcer," Surg., Gynec. and Obst., 1914, xix, 528–530.

TUBERCULOSIS OF THE STOMACH, WITH RE-PORT OF A CASE OF MULTIPLE TUBERCULOUS ULCERS*

ALBERT COMPTON BRODERS

Tuberculosis of the stomach was encountered only once in a series of 2501 gastric operations in the Mayo Clinic from the years 1912 to 1915 inclusive. The fact that in this instance resection was done supposedly for carcinoma with partial obstruction stimulated the following investigation of the literature.

HISTORIC

As nearly as could be ascertained, tuberculosis of the stomach was first mentioned by Barkhausen in 1824. From this date to the discovery of the specific organism by Koch in 1882 a fair number of cases were reported, the best report being that by Litten in 1876.

Litten's description is nothing short of classic. His case presented a single ulcer, 4.2 cm. by 3.2 cm. on the anterior wall, in the region of the lesser curvature, which on microscopic examination showed typical caseating tubercles with giant-cells containing peripherally situated nuclei.

In 1878 Breus gave a good gross and microscopic description of a case with ulcers and pyloric stenosis resulting from a firm scar.

In 1879 a good gross and microscopic description was published by Talamon of a case in a female child four and one-half years old, with seven ulcers scattered over the mucous surface from cardia to pylorus.

In 1881 Eppinger reported two interesting cases, both those of males, thirty and fifty-five years of age. A good gross and microscopic description (see Miliary Tuberculosis under types of lesions) accompanied this report also.

Regardless of the thoroughness with which the above-mentioned cases have been described, however, there is a certain element of doubt

* Reprinted from Surg., Gynec. and Obst., 1917, xxiv.

179

as to a positive diagnosis of tuberculosis because of the fact that the bacillus of tuberculosis was not discovered until 1882.

The first to demonstrate the specific organism in the walls of a gastric ulcer was Coats in 1886. Thereby he eliminated all doubt as to the etiology of the lesion. Since that time the specific organism has been demonstrated in a fair number of cases. It was first accomplished in the United States by Musser in 1890.

While from time to time a fairly large number of cases has been reported, the majority will not stand when put to a critical test.

Kühl, in 1889, reported 7 cases, 5 of the ulcer type and 2 with tubercles. He demonstrated the tubercle bacillus in 2 cases, 1 of each type. He also mentioned 7 other cases, but a microscopic examination was not made.

In 1897 Hamilton, after a critical but incomplete review of the literature, was able to find only 15 positive and 9 probable cases, to which she added 3 positive cases.

Blumer, in 1898, collected 30 authenic cases from the literature, to which he added 1 positive case.

Simmonds, in 1900, reported 8 ulcer cases and 4 of the miliary tubercle type.

Glaubitt, in 1901, reported 47 cases (40 of the ulcer type and 7 with tubercles) from 12,528 necropsies, 2237 of which were tuberculous, i. e., 0.38 per cent. of the total number of cadavers and 2.1 per cent. of those that were tuberculous.

Przewoski in 1902 reported 5 cases of tuberculous gastric ulcer, in all of which the tubercle bacillus was present.

In 1902 Arloing reported 147 cases he had collected from the literature with the exception of 1 personal case.

Ricard and Chevrier, in 1905, collected 107 cases in which the findings in 16 cases of tuberculous pyloric stenosis were reported. Four of these were personal cases. The authors of the two latter reports were not very critical and accepted a good many cases that should have been rejected or classified as doubtful.

TYPES OF LESIONS

After a thorough review of the literature it will be found that gastric tuberculosis may be divided into 6 types as follows: (1) Ulcer (single or multiple); (2) miliary tubercle; (3) solitary tubercle; (4) pyloric stenosis; (5) tumor or nodule (single or multiple); and (6) lymphangitis.

1. *Ulcer Single or Multiple.*—There is practically no difference between the tuberculous gastric and intestinal ulcer. Tuberculous gastric ulcers range in size from the slightest erosion to 20 cm. by 10 cm. (Glaubitt). Some are very shallow; others very deep, extending through to the serosa and even perforating. They vary in number from a single ulcer to large numbers. In her first case Hamilton reported from 115 to 120. Sometimes they are associated with miliary tubercles.

2. *Miliary Tubercles.*—Miliary tuberculosis of the stomach is usually associated with a general miliary tuberculosis. An interesting case of this type was reported by Wilms in a child nine months old. Wilms holds that miliary tuberculosis of the stomach may be frequently associated with general tuberculosis; that the postmortem changes in the stomach mucosa twelve or twenty-four hours after death are such as to obscure the miliary tuberculosis.

Simmonds believes that miliary tuberculosis of the gastric mucous membrane is not a rare occurrence.

In one of Eppinger's cases tuberculous ulcers and miliary tubercles of the stomach were associated with chronic tuberculosis in the upper lobe of the right lung. In the other case there was an old tuberculosis in the apex of the right lung, miliary tuberculosis of both lungs and liver, and tuberculous ulcers in the stomach. Eppinger concluded that in both cases the gastric tuberculosis was of a general acute type.

3. *Solitary Tubercle.*—The solitary tubercle is very rare. Van Wart reported an interesting case in which the tubercle, 3.5 cm. in diameter, was located 6 cm. from the cardiac orifice on the greater curvature. The same patient had small simple ulcers near the pylorus, chronic peritonitis, chronic pericarditis, chronic pleuritis, and bronchopneumonia. It was not possible to demonstrate tuberculosis in any organ other than the stomach. Van Wart concluded: "It is impossible to state whether the lesion was primary in the stomach, but there is no definite evidence to the contrary."

Another interesting case was reported by Barchasch. In this instance a solitary tubercle of the stomach was associated with tuberculosis of the lungs and lymph-glands with carcinoma of the cardia of the stomach and esophagus.

4. *Pyloric Stenosis.*—Tuberculous stenosis of the pylorus is of two types: the true and the false. The true type includes cases in which the pylorus is obstructed by an old tuberculous ulcer with an excessive amount of scar tissue and tuberculous granulations or by a diffuse, non-

ulcerative tuberculosis of the pylorus. A large number of cases have been reported as tuberculous stenosis of the pylorus when, as a matter of fact, they should come under the false type, the tuberculous process being extragastric. The stenosis of this type is brought about by enlarged tuberculous peripyloric lymph-glands, or by a tuberculous peritonitis in the region of the pylorus, accompanied by adhesions often involving other organs in the process. Both types have been described by Ricard and Chevrier.

5. *Tumor or Nodule (Single or Multiple).*—A case of this kind was described by Cone in which there were three types of nodules with a general acute miliary tuberculosis. The first type was due to a connective-tissue overgrowth or to irregular fibrous contraction and the second to an atypical glandular growth. The third was specifically tuberculous.

6. *Lymphangitis.*—Reports of tuberculous lymphangitis of the stomach are rare. A good case has been described by Dewey—that of a man forty-five years of age, who had, in addition to the gastric tuberculous lymphangitis, tuberculosis of the lungs, tuberculous tracheobronchial lymph-glands, and tuberculous ulcerative colitis. He was extremely emaciated, weighing only 64 pounds.

MODE OF INFECTION

The stomach may be infected with tuberculosis by at least four routes: (1) The mucosa (direct infection); (2) the blood-stream; (3) the lymphatic system; and (4) continuity and contiguity of structure.

It is safe to say that infection of the normal mucosa of the stomach is difficult. However, it seems reasonable to conclude that a lesion associated with reduced acidity renders such infection easier. It is a well-known fact that a good many tuberculous patients are afflicted with disease of the stomach.

Marfan found a terminal gastritis in 18 of 27 phthisical patients. A fair number suffer from simple gastric ulcers, such as the cases of Papellier (3 cases), Chambers, Cruveilhier, Toulmouche (5 cases), Heine, and others.

Happel and Blumer reported a case of advanced pulmonary tuberculosis accompanied by round ulcers of the stomach and an absence of free hydrochloric acid. While a microscopic examination of material scraped from the bases of the ulcers showed many tubercle bacilli, it was impossible to demonstrate the bacilli in the depths of the ulcers or to

find a histologic picture of tuberculosis. This case proves that in the absence of free hydrochloric acid tubercle bacilli may come in contact with an eroded area of the stomach and still not produce tuberculosis of the organ.

Cases have been reported in which the stomach was affected with both tuberculosis and cancer (Claude, Barchasch, second case, Lyle, Borst and Simmonds). In such instances it seems that it would be rather difficult to prove which was there first.

Various writers ascribe the gastric tuberculosis in the cases they report to the swallowing of sputum containing tubercle bacilli (Kühl, 7 cases; Ellis, first case, and others).

Dürck states that, in order to infect the mucosa, a break in the continuity of the mucosa and a neutralization or a lessening of the acidity of the gastric juice are necessary.

According to Birch-Hirschfeld, tuberculosis of the gastric mucosa may occur only when active tubercle bacilli attack an eroded area.

Hamilton suggested that in her second case ecchymoses may have been the forerunners of the small erosions, the tubercle bacillus being responsible only secondarily for the further destruction.

Wilms states that gastric ulcers may occur in the absence of tubercle bacilli, being due to embolic plugs in the vessels.

According to Arloing, the blood-stream is the most probable route of infection. He bases his opinion on the results of experimental work. Other authors also believe this to have been the route of infection in their cases (Cone, Wilms, Simmonds, 4 cases).

According to some writers, the lymphatic system plays an important part in gastric tuberculosis. Baumgarten believes that tuberculosis of the stomach always commences in the lymph-follicles, never in the mucosa or any other part of the wall.

Wilms states that lymph-follicles in the stomachs of children are very few in number, though they increase in adults; he also states that in his case the follicles were not responsible.

Barbacci considered the lymph-follicles the primary seat of infection. Dobrowolski has shown that the lymph-follicles are not always so few in the human stomach. In catarrhal gastritis they are markedly increased, and he has applied to this condition the term "gastritis granulosa" (see Marfan, under Mode of Infection).

That tuberculosis may enter the stomach from adjacent tuberculous lymph-glands is evident from the case of Claytor and Wilkinson, in

which the tuberculous glands were intimately fused with the base of a tuberculous gastric ulcer.

Chiari had a similar case.

Rosset thought that in his case the tuberculosis was primary in the lymph-glands at the hilus of the left lung, and that it infected the retro-gastric lymph-glands and then the stomach by a blockade of the lymph-stream. This patient had a tuberculous ulcer of the cardia.

Tubercle bacilli may enter the lymphatics of the stomach and set up a tuberculous lymphangitis, as was proved in Dewey's case by the find-ing of the bacilli in the lymph-vessels and tuberculous ridges following the lines of these vessels.

Infection by continuity and contiguity of structure is believed by some to be important.

Rokitansky stated that tuberculosis of the stomach occurs as a result of intestinal tuberculosis which has advanced to an extreme degree (con-tinuous involvement). In his opinion the lymph-glands of the stomach bear the same relation to tuberculosis of that organ as the mesenteric glands bear to tuberculosis of the intestines. His first statement has not proved entirely correct, as cases of gastric tuberculosis have been described in which the intestines were entirely free from tuberculosis (Litten, Eppinger (2 cases), Brechemin, Mathieu and Rémond, Van Wart, Lyle, Gossmann, and the writer).

Dürck stated that very probably a large number of the reported cases of tuberculous ulceration of the stomach are due to the entrance of the bacilli, not from the inside, but from the peritoneal surface, because of a general or local peritonitis. Ellis' second case is an example.

It is possible for the stomach to become infected with tuberculosis by direct extension from adjacent organs, such as occurred in the case reported by Winternitz.

In a number of instances infection by the lymph-stream and by con-tinuity and contiguity of structure is indistinguishable.

RELATIVE IMMUNITY

In 1879 Orth, by feeding tuberculous material to rabbits, was able to produce tuberculosis in various parts of the body. The lymph-glands were involved 7 times out of 9. In the stomach he found hemorrhagic erosions twice and an ulcer once. This ulcer was only 7 or 8 mm. in diameter. From his microscopic description the ulcer was probably not tuberculous.

In 1883 Falk took particles from tuberculous lungs and caseous particles and pus from cavities, immersed them in the digestive juices, and injected them into the peritoneal cavities of guinea-pigs. The result, except for a local reaction, was negative. He then allowed the tuberculous material to putrefy and still obtained a negative result. Next, he took tuberculous material from bodies that had been dead for eight days and kept at medium temperature, but found that it had lost its virulence to a certain degree. He produced tuberculosis by injecting into a guinea-pig a piece of tuberculous material which had been obtained from a cow and soaked in gastric juice for several days.

Frank, in 1884, took small pieces of tuberculous lung, let them stand in water for twenty-four hours, stained some of the fluid with Ehrlich's stain, and found tubercle bacilli in great numbers. He then made up the following solutions with the solution containing the tubercle bacilli: (1) 1:1000 pepsin; (2) 1:2000 pepsin plus 0.05 of 1 per cent. to 0.1 of 1 per cent. HCl; (3) 0.05 to 0.1 per cent. HCl; and (4) 0.3 of 1 per cent. bile.

The above solutions were incubated at from 37° to 38° C., and after from one to six hours 5 to 8 c.c. of each were injected into the peritoneal cavities of rabbits and guinea-pigs. At the same time some of the original solution was injected into rabbits as a control. Those that died before seventeen days after inoculation showed no tuberculous infection. After that time they showed definite symptoms, and all that were killed or died after six weeks showed general tuberculosis. The strength of the formulas was increased with the same result. According to Frank, these experiments showed two facts: (1) That the material was really infectious; and (2) that pepsin, HCl, and bile had no effect.

Sormani, in 1884, concluded that the bactericidal action of gastric juice on tubercle bacilli is efficient, and that gastric diseases cause this action to disappear.

Wesener, in 1885, placed tuberculous particles in artificial gastric juice at 38° C. for some hours. He then inoculated the cecum of rabbits, obtaining positive results. Five injections of the same material into the anterior chamber of the eye also proved positive.

Fischer, in 1886, concluded that the gastric juice is inefficient.

Zagari, in 1889, fed dogs for three or four months on material containing many bacilli that had been obtained from phthisical patients; he fed them also organs from tuberculous animals. He recovered numerous bacilli in the feces that were active for guinea-pigs. In his opinion the bacilli went through the digestive tube of the dog without notice-

able change because of their short stay in the stomach. In vitro and at 38° C. the bacilli put in contact with the gastric juice of a dog containing 0.1652 free HCl per 1000 for three or four hours were still very virulent. After seven, eight, and nine hours they produced only a local glandular tuberculosis, and after eighteen to twenty-four hours of contact they were without action.

Straus and Würtz, in 1889, mixed in vitro pure gastric juice of a dog with a young and virulent culture of tubercle bacilli. Tubes containing 1 c.c. of gastric juice mixed with the culture were put in an oven at 38° C. for a time varying from one to forty-eight hours. Rabbits that were inoculated by the contents of tubes that had remained in the oven from one to six hours died with generalized tuberculosis; those that were inoculated with the contents after eight to twelve hours in the oven developed only a local abscess without any tendency to generalization (the bacilli were dead or attenuated). The bacilli lost all activity if they remained in the oven more than eighteen hours.

Kurloff and Wagner, in 1890, added to artificial gastric juice tubercle bacilli from cultures or tuberculous masses and placed the bacilli in the stomach of dogs through previously made fistulas. The results were negative even after seven hours of contact.

In 1896 Kjianowski arrived at the same conclusion as to the viability of the bacilli.

Schoull, in 1891, proved that the gastric juice of cats is not bactericidal.

Cadéac and Bournay, in 1893, at the Veterinary School of Lyons, conducted experiments to ascertain the bactericidal action of the digestive juices and the possibility of contagion by fecal matter. They found that digestion in vitro had not the same value as digestion in life. It was their aim to approach the natural means of contagion. They believe that the bactericidal power of the gastric juice in vivo is considerably modified by dilution with fluids, absorption by food, and neutralization by saline substances. Their experiments demonstrated the complete inefficiency of the gastric juice.

Carrière, in 1901, found that artificial gastric juice mixed in vitro at 37° C. with three- to twenty-four-hour cultures of tubercle bacilli or in milk particles or food containing the bacilli remained without action on them if the contact did not last at least twelve hours. After twelve hours the food was still tuberculigenic, the bacilli being only attenuated, not killed. He took gastric juice from a healthy man, added the same

infected particles to it for twelve hours at 37° C., with the result that the virulency of the bacilli was attenuated.

Arloing, in 1902, performed 3 series of experiments on 30 animals (2 calves, 13 dogs, 1 sheep, 11 rabbits, and 3 guinea-pigs). In his first series he introduced human tubercle bacilli from a young culture by injecting them into the stomach through a fistula or inoculating them into the mucosa of the organ of seven animals. The experiments lasted from two to two and a half months, and were terminated most often by the sacrifice of the subject; more rarely by death. In this series Arloing increased the acidity of the gastric juice, introduced alkaline solution into the stomach, ligated five or six arteries along the greater curvature from cardia to pylorus, produced mechanical ulcerations of the mucosa with the electric needle and also an ulceration of the mucosa by the injection of an emetic before introducing the bacilli. He was unable to produce a tuberculous gastric ulcer in a single instance.

In his second series he utilized the intravascular method of injecting the tubercle bacilli, using 1 calf, 2 dogs, and a rabbit. Gastric ulcers resulted in all the animals, but they were not definitely tuberculous. He was able to produce two tuberculous duodenal ulcers in one of the dogs. All the animals in this series showed polyvisceral miliary lesions.

In his third series he introduced human bacilli in all cases by interstitial inoculation of the stomach of 1 calf, 1 sheep, 4 dogs, 10 rabbits, and 3 guinea-pigs. In the stomach of the sheep he found a tuberculous mass filled with tubercle bacilli at the point of injection. In one of the dogs he produced a typical tuberculous gastric ulcer with tubercle bacilli in its subjacent tissue. He was able to produce the types of tuberculous ulcerations found in man, twice in 30 animals—once in the stomach and once in the duodenum, both times in dogs. The first time injection of the bacilli into the blood-stream produced tuberculous ulcers of the duodenum, and the second time injection into the wall of the stomach produced a tuberculous gastric ulcer.

Various theories have been advanced regarding the relative immunity of the stomach to tuberculosis. Some of these are as follows:

Dürck believed that the stomach is protected fairly well in normal persons by the strong acidity of its juice, but that tubercle bacilli are not killed by this strong acid, as is proved by the prevalence of intestinal tuberculosis and by many experiments.

Virchow ascribed the rarity of gastric tuberculosis to the sparcity of the lymphatic supply of the stomach-wall.

Klebs ascribes its rarity to the sparcity and deep-seated location of the lymph-follicles.

Kanzow states that the main reason is not only the sparcity and the deep location of the lymph-follicles, but an intact condition of the epithelium and the relatively short stay of the ingesta in the stomach.

Struppler also believes that the intact epithelium acts as a protection against tubercle bacilli, although he admits that they may attack the lymph-follicles without injuring the epithelium.

In Simmonds' opinion the normally secreting mucosa plays an important rôle.

Other organs are known to be relatively immune to tuberculosis: the thyroid, salivary glands, esophagus, pancreas, gallbladder, ovary, uterus, and heart.

Arloing mentioned the resistance of muscle tissue to tuberculosis. Probably such resistance accounts for the relative immunity of the uterus and heart, muscle being the predominating tissue in both.

CLASSIFICATION OF CASES

In order to draw correct conclusions from the cases that have been reported in the literature, it is necessary to make a classification from a critical standpoint. For convenience the cases are grouped under four classes: (1) Positive; (2) probable; (3) doubtful; and (4) rejected. The qualifications for each class are as follows:

1. *Positive.*—All cases that contain a histologic picture of tuberculosis plus the presence of the bacillus of tuberculosis in the depths of the lesion or the presence of the specific bacillus in the depths of an indefinite histologic lesion.

2. *Probable.*—All cases that possess a histologic picture of tuberculosis.

3. *Doubtful.*—All cases with a good gross description of tuberculosis or a good gross description plus a poor histologic description.

4. *Rejected.*—All cases that cannot meet the qualifications of the three preceding classes, i. e., cases regarding which is given only a clinical diagnosis, a poor gross description, a poor gross and microscopic description, the mere statement (unaccompanied by a positive histologic picture) that tubercle bacilli were present on the surface of the lesion and mere statements as to the nature of the condition without substantiation of their claims; also case of the false type of tuberculous pyloric stenosis, etc.

CLASSIFICATION OF CASES

AUTHOR	POSITIVE	PROBABLE	DOUBTFUL	REJECTED
Alessandri	..	1	..	..
Alexander	..	1	..	..
Andral	..	..	..	2
Anger	..	..	1	..
Arloing	..	..	1	..
Barbacci	..	1	..	..
Barchasch	1	1	..	..
Barkhausen	..	..	..	1
Barlow	..	..	1	..
Baron	..	..	..	1
Barth	..	1	..	..
Batsère	..	1	..	..
Beadles	..	1	..	..
Bednar	..	..	..	1
Beneke	..	..	1	..
Besnier	..	..	1	..
Bignon	..	..	1	..
Blas	1	3	..	..
Blumer	1	..	..	..
Borst	1	..	..	..
Brechemin	..	1	..	..
Breuer	..	..	..	1
Breus	..	1	..	..
Cazin	..	..	1	..
Chalier and Nové-Josserand	..	1	..	..
Chevassu	..	..	..	1
Chiari	..	1	..	..
Chvostek	..	..	4	..
Clairmont	..	..	..	2
Claude	1	..	..	..
Claytor and Wilkinson	1	..	..	..
Coats	1	..	..	..
Cone	1	..	..	..
Curschmann	..	1	..	..
Czerny	..	1	..	..
DaCosta	..	..	1	..
Dauwe	..	..	1	..
DeVecchi	1	..	..	..
Devic	..	..	..	1
Dewey	1	..	..	..
Docq	..	1	..	..
Duguet	..	..	1	..
Durante	..	2	..	..
Ellis	2	..	..	..
Eppinger	..	2	..	..
Ferrari	..	..	..	1
Fischer (Erwin)	..	..	..	1
Fischer-Defoy	..	1	..	..
Fox	..	..	1	..
Frerichs	..	..	6	..
Frommer	..	..	..	2
Fujii	..	..	1	..
Gaillard	..	..	1	..
Gelpke	..	1	..	..
Glaubitt	1	46	..	..
Godart-Danhieux	..	..	..	2
Gossmann	..	3	..	1

CLASSIFICATION OF CASES—(*Continued*)

AUTHOR	POSITIVE	PROBABLE	DOUBTFUL	REJECTED
Habershon	1	..	..	..
Hamilton	3	..	..	..
Hanau	..	..	1	..
Hattute	..	..	1	..
Hebb	..	1	..	..
Hecker	..	..	..	2
Herczel	..	1	..	..
Holt	3	..	2	..
Holzmann	1	3	..	..
Jacobs	..	..	..	1
Kanzow	..	1	..	..
Keen	..	..	1	..
Klebs	..	..	1	..
Kühl	2	5	..	7
Kundrat	..	..	2	..
Labadie-Lagrave	..	..	..	1
Lancereaux	..	..	..	1
Lange	..	..	1	..
Lava	..	1	..	..
Letorey	..	1	..	..
Letulle	1	..	..	..
Leven	..	..	..	1
Lipscher	..	1	..	..
Lister	..	2	3	..
Litten	..	1	..	..
Lorey	..	..	1	..
Louis	..	..	..	1
Lyle	..	1	..	..
Margarucci	..	1	..	..
Mathieu	..	1	..	..
Mathieu and Rémond	1	..	..	..
Mayo-Robson and Moynihan	..	..	1	..
Melchior	..	6	..	..
Merry	..	..	..	1
Mouisset and Mouriquand	..	..	..	1
Müller	..	..	..	5
Musser	1	..	..	..
Nash	..	..	1	..
Nordmann	1	..	..	..
Oppolzer	..	..	1	..
Papavoine	..	..	1	..
Patel	..	..	..	1
Patella	..	..	..	3
Paulicky	..	..	1	..
Petruschky	..	..	..	2
Pitt	..	..	..	1
Plambeck	..	..	..	3
Pozzi	..	..	1	..
Przewoski	5	..	..	..
Quénu	..	..	..	1
Reinhold	1	..	..	..
Rémon-Verliac	1	..	..	..
Ricard	..	..	1	1
Ricard and Chevrier	..	..	..	2
Rilliet and Barthez	..	..	..	21

CLASSIFICATION OF CASES—(*Continued*)

AUTHOR	POSITIVE	PROBABLE	DOUBTFUL	REJECTED
Roger	..	..	..	1
Rosset	..	1	..	..
Ruge	1	..	..	..
Satterthwaite	..	..	..	2
Schede	1	..	..	..
Schlesinger	..	1	..	..
Serafini	1	..	..	..
Sigg	..	1	..	..
Simmonds	1	11	..	..
Steiner and Neureutter	..	..	4	..
Stelter	..	..	5	..
Still	2	1	2	..
Sokolowski	1	..	..	..
Struppler	..	..	1	..
Talamon	..	1	..	..
Thorel	3	1	1	..
Tichoff	..	1	..	..
Tripier	..	1	2	2
Vallas	..	1	..	..
Van Wart	1	..	..	..
Von Tappeiner	..	..	1	..
Weinberg	1	..	..	..
Widerhofer	..	..	..	2
Wilms	1	..	..	..
Winternitz	1	..	..	..
Personal	1	..	..	..
Total	49	118	59	80

STATISTICS COMPILED FROM POSITIVE CASES

Adults	33
Children	12
Not indicated	4
	49

Males	24
Females	14
Not indicated	11
	49

TYPES OF LESIONS

Single ulcer	14
Single ulcer and miliary tubercles	1
Single ulcer and nodules	1
Single ulcer and carcinoma	1
Multiple ulcers	19
Multiple ulcers and miliary tubercles	3
Multiple ulcers and carcinoma	1
Miliary tubercles	3
Solitary tubercle	2
Solitary tubercle and carcinoma	1
Tumors or nodules	2
Lymphangitis	1
	49

Total ulcer cases, 40 out of 49 (81.6 per cent.).

The tuberculous process has been considered primary in the stomach 4 times (Lava, Ruge, Fischer-Defoy, and Van Wart).

Lava's patient had tuberculosis of the intestines and lymphatic glands in the pyloric region, accompanied by an acute diffuse serofibrinous peritonitis and a chronic peritonitis.

Ruge's patient had tuberculosis of the pleura, intestines, peritoneum, right kidney, and of the omental, para-aortic, and inguinal lymphatic glands.

In the case described by Fischer-Defoy there was tuberculosis of the lungs, intestines, and lymphatic glands of the lesser curvature of the stomach and in the region of the liver. According to the author, the older process was in the stomach and intestinal tract, but there was no exact proof that it was primary in the intestine.

Van Wart was unable to demonstrate tuberculosis in any other part of the body, although the patient had chronic peritonitis, pleuritis, and pericarditis. It was impossible to state whether the lesion was primary in the stomach, but there is no definite evidence to the contrary.

The cases of the first three authors cited should not be classified as primarily gastric. The only case which could be considered primary in the stomach is that of Van Wart, who stated: "The autopsy revealed no other definite tuberculous lesion, but the nature of the process giving rise to the peritonitis, pleuritis, and pericarditis, must be considered."

No case of tuberculosis should be considered primary in the stomach unless a thorough search does not show any evidence of the disease in any other part of the body.

CASE REPORT

F. P., male, aged forty-two years, bricklayer. Married eleven years. One child who died at the age of one year from meningitis. Patient had no previous diseases of note. Chief complaint, stomach trouble. Operated on six months previously elsewhere; incision closed; diagnosis of inoperable carcinoma of stomach. *Clinical history:* Trouble began two years previously with a feeling of heaviness in the epigastrium which

came on from one-half to two hours after meals. Six months later he began to have attacks of vomiting every two or three days from two to three hours after meals. Nine months previous to coming for examination he ceased vomiting for two months but there was no cessation of the epigastric distress. Six months previously there was recurrence of vomiting, almost daily, about one-half an hour after meals. Patient lost weight rapidly. Six months prior to coming to the Clinic an exploratory operation was done after which there was some improvement for five months. For the past three weeks regurgitation occurred as soon as food was taken. The patient could retain eggnog. He never had severe pain or sour stomach. Always felt hungry. *Physical examination:* Nothing of note except a mass in the right side of the upper abdomen. *Preoperative laboratory findings:* Hemoglobin, 70 per cent.; erythrocytes, 4,760,000. Test-meal: Total acidity, 12, all combined;
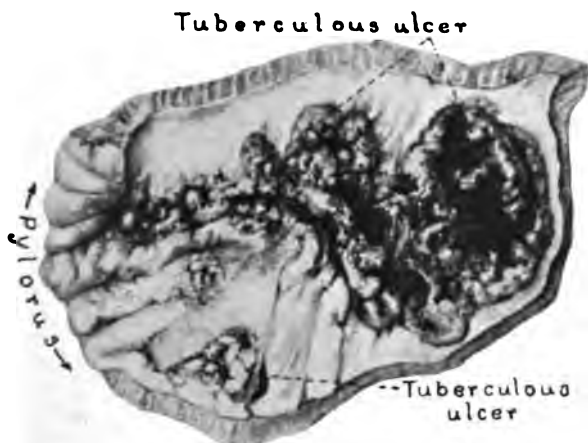
Fig. 102.—(Case 152,198.) Multiple tuberculous gastric ulcers. Drawing of gross specimen.

food remnants, 1 on a basis of 4; filtrate, 150 c.c. Oppler-Boas 1 on a basis of 4. *Roentgenologic report:* Carcinoma of stomach, operable. *Clinical diagnosis:* Carcinoma of the stomach. *Operation:* Polya resection; about one-third of stomach removed; high midline incision (E. S. Judd). Tumor of stomach near pylorus; marked spasm but stomach not dilated.

Post-operative Laboratory Findings.—Macroscopic: Pyloric third of stomach containing three yellowish-brown ulcers with ragged edges and dirty rough bases on mucous surface (Figs. 102 and 103). The larger ulcer extends from a point 1.5 cm. from the pyloric ring upward on the greater curvature for 7 cm. It is 4 cm. in width. The two smaller ulcers are 1 cm. in diameter. One is situated 2.5 cm. from the pyloric ring and 7 cm. from the large ulcer; the other is 3 cm. from the pyloric ring and 3 cm. from the large ulcer.

Microscopic: Sections from all of the ulcers show typical tubercles with characteristic giant-cells, extending down to the musculature (Figs. 104 and 105). Paraffin sections stained by the Ziehl-Neelsen method show a few scattered tubercle bacilli in the depths of the ulcers (Fig. 106). A thorough search for spirochetes was made but the findings were negative. A few of the lymphatic glands attached to the resected portion of the stomach are slightly enlarged and on gross section are of a yellowish-brown color. Microscopically they show typical tubercles and giant-cells. These glands apparently are in the precaseous stage.

Fig. 103.—(Case 152,198.) Photograph of gross section shown in Fig. 102.

Three sputum examinations were all negative to acid-fast bacilli. von Pirquet test negative. Complete blood count one day after operation: Hemoglobin, 82 per cent.; erythrocytes, 5,440,000; leukocytes, 23,400; differential, total number, 300; polymorphonuclear neutrophiles. 88; small lymphocytes, 10 per cent.; large lymphocytes, 1.7 per cent.; basophiles, 3. White blood count three days after operation: Leukocytes, 15,800; differential, total number, 300; polymorphonuclear neutrophiles. 90.3 per cent.; small lymphocytes, 6.7 per cent.; large lymphocytes, 3 per cent. White blood count six days after operation: leukocytes, 9200; differential, total number, 300; polymorphonuclear neutrophiles. 83.7 per cent.; small lymphocytes, 10.7 per cent.; large lymphocytes, 5.3 per cent.; eosinophiles, 0.3 per cent.

Wassermann test six days after operation: Total inhibition.

Patient died eleven days after operation. *Clinical cause of death:* Pneumonia.
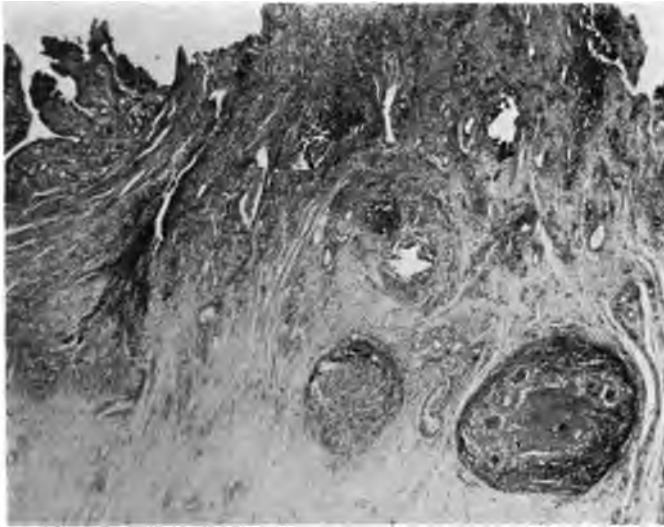
Fig. 104.—(Case 152,198.)   Photomicrograph of section of large ulcer at juncture of base and border, showing one definite and three indefinite tubercles (low power).
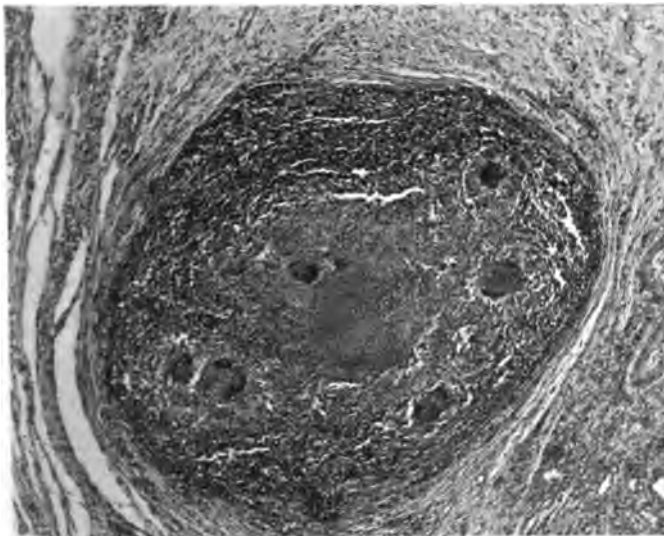
Fig. 105.—(Case 152,198.)   Definite tubercle, Fig. 104, showing six giant-cells (high power).

Necropsy (One and One-half Hours after Death): An extremely emaciated white man about middle age; 5 feet, 8 inches in height, and weighing about ninety pounds. Findings negative except for an upper midline abdominal incision, 14 cm. long, with edges in good apposition. On section of the thorax firm pleural adhesions at both apices and a recent fibrinous pleurisy over the lower lobe of the right lung were encountered. At the apex of the left lung was an area of old tuberculosis measuring 5 by 7 by 5 cm., and characterized by fibrosed, dry and caseous tubercles. Throughout the remainder of this lung, as well as the lower lobe of the right lung, were scattered areas from miliary size to 2 cm. in diameter. showing various stages of the tuberculous process. The peribronchial lymph-glands were enlarged. The heart was small, weighing only 210

Fig. 106.—(Case 152,198.) Tubercle bacillus in the depths of the large gastric ulcer (× 1400).

gm. Except for apparent myocardial degeneration, it was normal. About one-third of the pyloric end of the stomach had been resected and there was a clean anastomosis between the remainder and a loop of the jejunum. In the gastrocolic omentum were several hard nodules about the size of a pea, probably tuberculous glands. The retroperitoneal glands in the region of the stomach were enlarged. The intestines were absolutely free from tuberculosis. The liver showed a fairly marked fatty change. In the remainder of the abdominal viscera the pelvic viscera, and the genitalia, there was nothing of note.

Anatomic diagnosis: Recent tuberculosis of the lower lobes of both lungs with an old tuberculous process in the left upper lobe. An acute fibrinous pleurisy of the right side and an old adhesive pleurisy of the left. Myocardial degeneration, fatty changes in the liver, and tuberculous lymphadenitis.

Microscopic examination: In the apex of the left lung was an old tuberculous process characterized by a marked fibrosis, in addition to the typical picture of tuberculosis (Fig. 107). In sections from the depths of the lower lobes of the lungs stained by the Ziehl-Neelsen method numerous tubercle bacilli were found (Fig. 109). Sections from the peribronchial lymph-glands showed typical tuberculosis not yet broken down. Sections from the remainder of the stomach showed no tuberculosis. Sections from the lymph-glands in the gastrocolic omentum showed tuberculosis. The liver showed a marked fatty change. In the
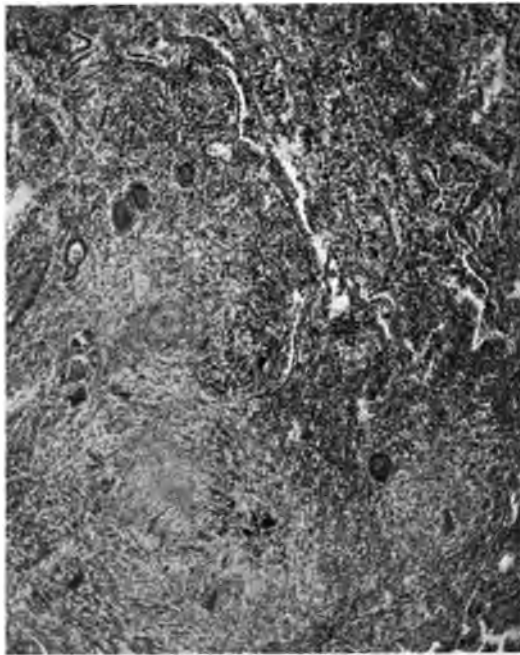
Fig. 107.—(Case 152,196.)   Photomicrograph of section of the apex of the left lung, showing giant-cells, necrotic areas, scar tissue, and round-cells.

remainder of the organs there was nothing of significance. In a smear from a freshly cut surface of the lower lobe of the left lung stained by the Ziehl-Neelsen method were numerous tubercle bacilli (Fig. 108).

A Wassermann test from the blood at necropsy showed a total inhibition.

SUMMARY AND CONCLUSIONS RELATIVE TO THE CASE REPORT

1. The clinical history suggested a gastric ulcer or carcinoma.

2. There was no sign or symptom in the clinical history suggesting disease of the chest, so completely did the gastric symptoms predominate.

3. The failure to detect the lesion in the apex of the left lung by the physical examination was probably due to the absence of cavity formation.

Fig 108.—(Case 152,198.)   Tubercle bacilli in smear from cut surface of the left lung (× 1800).

Fig. 109.—(Case 152,198.)   Two tubercle bacilli in the depths of the lung tissue, end-to-end (× 1600).

4. Three sputum examinations following the operation failed to throw any light on the pulmonary condition.

5. In all probability the source of infection in this case was the old tuberculous lesion in the upper lobe of the left lung.

6. The tuberculosis of the peribronchial lymphatic glands and the lymphatic glands adjacent to the stomach were probably secondary to tuberculosis of the upper lobe of the left lung and the stomach respectively.

7. If the Wassermann test is infallible in the presence of advanced tuberculosis this patient had syphilis, but whether it was infallible or not, the outstanding fact is that the patient had gastric and pulmonary tuberculosis, as was proved by a definite histologic picture and the finding of the bacillus of tuberculosis in the depths of the lesions.

GENERAL CONCLUSIONS

1. Little was known of gastric tuberculosis before the middle of the nineteenth century.

2. Gastric tuberculous lesions have practically the same gross and microscopic appearance as tuberculous lesions of the intestines.

3. A specific reason for the relative immunity of the stomach to tuberculosis still remains unknown.

4. The gastric juice appears to have a very slight effect on the tubercle bacillus unless the contact extends over a period of at least twelve hours.

5. It is possible to produce gastric tuberculosis experimentally.

6. The exact mode of infection is often difficult to determine.

7. The theory that gastric tuberculosis is always secondary to intestinal tuberculosis has been disproved.

8. About half of the cases reported as gastric tuberculosis should be classified as doubtful or rejected.

9. Adults are affected more often than children, the ratio being about 3:1.

10. Males are affected more often than females, the ratio being about 2:1.

11. Ulcer is the predominating lesion in the positive and probable cases, constituting 81.6 per cent. of the former and 80.5 per cent. of the latter.

12. In the positive cases the lesser curvature is the most frequent

site of the ulcer or ulcers, the pylorus leading in the probable cases and in a combination of the positive and probable cases.

13. In tuberculosis of other organs associated with gastric tuberculosis the lungs take the lead, closely followed by the intestines.

14. No case of tuberculosis of the stomach has been absolutely proved to be primary in the stomach.

REFERENCES

Alessandri: "Académie de medécine de Rome," abst. in Presse méd., June 3, 1905. Cited by Brunner, loc. cit., p. 30.

Alexander: "Beitrag zur Tuberculose des Magens," Deutsch. Arch. f. klin. Med., 1906, lxxxvi, 212–216.

Andral, G.: A Treatise on Pathological Anatomy, 1830, vol. 2, p. 127.

Anger, T.: Soc. de chir., 1878. Cited by Letorey, loc. cit., p. 39.

Arloing, F.: "Des ulcérations tuberculeuses de l'estomac (étude clinique, experimentale et anatomo-pathologique)," Thèse de Lyon, 1902.

Barbacci, O.: "Una rara forma di tuberculosi gastrica," Sperimentale, 1890. Cited by Ricard and Chevrier, loc. cit., ii.

Barchasch, P.: "Zur Pathologie der Magentuberkulose. Tuberkulöse Pylorusstenose und solitärer Tuberkel des Pylorus," Beitr. z. Klin. d. Tuberk., 1907.

Barkhausen: Nye hygea of otto, Copenhagen, 1824. Cited by Arloing, loc. cit.

Barlow, T.: "Ulcers of the Stomach in a Child the Subject of General Tuberculosis," Tr. Path. Soc. London, 1887, xxxviii, 141–142.

Baron: Recherches, observations et expériences sur le développement naturel et artificial des maladies tuberculeuses, Tr. by Boivin, 1825. Cited by Marfan, loc. cit.

Barth: "Tuberculose du voile du palais et des amygdales," Thèse de Paris, 1880. Cited by Marfan, loc. cit.

Batsère, G.: "Les ulcérations tuberculeuses de l'estomac," Thèse de Toulouse, 1901. Cited by Arloing, loc. cit.

Baumgarten: Cited by Ricard and Chevrier, loc. cit., i, 573.

Beadles, C. F.: "Tuberculosis of the Stomach," Brit. Med. Jour., 1892, ii, 735.

Bednar: Die Krankheiten der Neugeborenen und Säuglinge, Wien, 1853. Cited by Widerhofer, loc. cit., p. 445.

Beneke: Analyse dans Virchow-Hirsch's Jahresbericht, 1851, iii, 260. Cited by Arloing, loc. cit.

Besnier: "Perforation de l'estomac produite de dehors en dedans par ouverture d'un abcès tuberculeux d'un des ganglions abdominaux," Bull. Soc. anat. de Paris, 1897, p. 115. Cited by Arloing, loc. cit.
"Ulcération de l'estomac suivie de perforation et de péritonite généralisée et accidents de tympanisme intenses," Bull. Soc. anat. de Paris, 1866, p. 97. Cited by Arloing, loc. cit.

Bignon: "Hématémèse mortelle, suite d'une perforation de l'estomac chez un enfant de 6 ans ½," Bull. Soc. anat. de Paris, 1853. Thèse de Paris, 1854. Cited by Letorey, loc. cit., pp. 27–30.

Birch-Hirschfeld: Lehrbuch der pathologischen Anatomie, 1894, pp. 641–643.

Blas, M.: "Ueber tuberculöse Geschwüre des Magens," Inaug. Dissert., München, 1896. Cited by Arloing, loc. cit.

Blumer, G.: "Tuberculosis of the Stomach with Report of a Case of Multiple Tuberculous Ulcers of That Organ," Albany Med. Ann., 1898, xix, 145.

Borst: "Carcinoma of Stomach with Multiple Tuberculous Ulcers," cited by Lyle, loc. cit., p. 695.

Brechémin, G.: "Ulcération de l'estomac," Bull. Soc. anat. de Paris, 1879, p. 452. Cited by Letorey, loc. cit., pp. 48–50.

Breuer, R.: "Demonstrirt einen Fall von Achylia gastrica mit tuberculösen Darmgeschwüren und eigenthümlichem durch Resorption vom Magen aus bedingtem Fieber," Wien. klin. Rundschau, 1902, xvi, 90–91.

Breus: Wien. med. Wchnschr., 1878, xxviii, 11. Cited by Arloing, loc. cit.

Brunner, C.: "Tuberculose, Aktinomykose, Syphilis des Magen-Darmkanals," Deutsch. Chir., 1907, xlvi, 3–37.

Cadéac and Bournay: "Rôle microbicide des sucs digestifs sur le bacille de Koch et contagion par les matières fécales," Compt. rend. Soc. de biol., 1893, p. 599. Cited by Arloing, loc. cit.

Carrière: "Action du suc gastrique sur les bacilles de la tuberculose," Compt. rend. Soc. de biol., 1901, p. 1098. Cited by Arloing, loc. cit.

Cazin: "Contribution à l'étude des tuberculisations vicérales. Des tubercules de l'estomac spécialement chez l'enfant," Soc. Méd. des Hôp., Paris, 1880 (Rapp. de M. Fernet). Cited by Letorey, loc. cit., pp. 50–52.

Chalier, J., and Nové-Josserand, L.: "Tumeur inflammatoire sténosante du pylore d'origine tuberculeuse," Lyon chir., 1911, vi, 389–412.

Chambers, T. K.: "On Ulceration of the Stomach and of the Esophagus," London Jour., 1852, iv, 587. Cited by Arloing, loc. cit.

Chevassu: "Sténose du pylore par compression ganglionnaire," Bull. et mém. Soc. anat. de Paris, 1902. Cited by Ricard and Chevrier, loc. cit., ii, 94.

Chiari, H.: "Ueber einen Fall von Perforation des Magens durch tuberkulose Lymphdrüsen," Wien. med. Wchnschr., 1878, xxi, 650–651.

Chvostek: "Ueber Tuberculose des Magens," Wien. med. Bl., 1882, v, 198–199; 234–235.

Clairmont, P.: "Bericht über 258 von Prof. v. Eiselsberg ausgeführte Magenoperationen," Arch. f. klin. Chir., 1905, lxxvi, 253–255.

Claude: "Infection tuberculeuse d'un cancer de l'estomac," Compt. rend. Soc. de biol., 1899, p. 112. Cited by De Vecchi, loc. cit.

Claytor and Wilkinson: "Tuberculous Ulcer of the Stomach, with Report of a Case," Arch. Int. Med., 1908, i, 285.

Coats, J.: "A Case of Tuberculosis of the Stomach," Glasgow Med. Jour., 1886, xxvi, 53.

Cone, C.: "Multiple Hyperplastic Gastric Nodules Associated with Nodular Gastric Tuberculosis," Rep. Johns Hopkins Hosp., 1900, ix, 877–890.

Cruveilhier: "Maladies de l'estomac. Considérations générales sur les ulcérations folliculeuses de l'estomac," Atlas d'anat. pathol. du corps humain, 1831, ii. Cited by Arloing, loc. cit.

Curschmann, H.: "Klinischer Beitrag zur Tuberkulose des Pylorus," Beitr. z. Klin. d. Tuberk., 1903–4, ii, 127–140.

Czerny: In Petersen and Machol: "Beitrag zur Pathologie und Therapie der gutartigen Magenkrankheiten," Beitr. z. klin. Chir., xxx, p. 330. Cited by Brunner, loc. cit., p. 31.

DaCosta, J. C.: "Surgical Tuberculosis," in Keen's Surgery, 1906, vol. 1, p. 656.

Dauwe, F.: "Contribution à l'étude de la tuberculose sténosante du pylore (granulome)," Arch. d. mal. de l'app. digestif, 1913, vii, 218–224.

De Vecchi, B.: "Tuberculosi gastrica," Clin. med. ital., 1902, xli, 103–116.

Devic: Cited by Arloing, loc. cit.

Dewey, K. W.: "Tuberculosis of the Stomach with Extensive Tuberculous Lymphangitis," Jour. Infect. Dis., 1913, xii, 236–248.

Dobrowolski: Beitr. z. path. Anat. u. z. allg. Path., 1894, xvi. Cited by Winternitz. loc. cit.

Docq: (Cité in Prov. méd., Nov. 30, 1907.) Cited by Leriche and Mouriquand, loc. cit., p. 530.

Duguet: Méd. des Hôp. de la Faculté, 1878, p. 172. Cited by Letorey, loc. cit., p. 39.

Durante: "Sténose tuberculeuse del pylore," Policlinico, 1894, No. 15. Cited by Ricard and Chevrier, loc. cit., ii, 91.

Dürck, H.: "Tuberkulose," Ergeb. d. allg. Pathol. u. path. Anat. d. Menschen u. d. Tiere, 1895, ii, 334–336.

Dürck, H., and Oberndorfer, S.: "Tuberkulose," Ergeb. d. allg. Path. u. pathol. Anat. d. Menschen u. d. Tiere, 1899, vi, 367–369.

Ellis, A. G.: "Tuberculous Ulcers of the Stomach," New York Med. Jour., 1910, xci, 546–547.

Eppinger: Prag. med. Wchnschr., 1881, vi, 501–502; 509–513.

Falk: "Ueber das Verhalten von Infectionsstoffen im Verdauungskanale," Virchow's Archiv. f. path. Anat., 1883, xciii, 177.

Ferrari: (Rapporté par Alessandri, 1902.) Cited by Leriche and Mouriquand, loc. cit., p. 531.

Fischer: "Ueber die Uebertragbarkeit der Tuberkulose durch die Nahrung, etc.," Arch. f. exper. Path. u. Pharmakol., 1886, xx, 446. Cited by Arloing, loc. cit.

Fischer, E.: "A Case of Tubercular Ulcer of the Stomach," Philadelphia Med. Jour., 1901, viii, 606–607.

Fischer-Defoy, W.: "Ausgedehnte Magentuberkulose," Centralbl. f. allg. Pathol. u. path. Anat., 1906, xvii, 4–6.
Fox, W.: "Tubercle of the Stomach," in Reynolds: A System of Medicine, 1872, ii, 993.
Frank, E.: "Ueber das Verhalten von Infectionsstoffen gegenüber den Verdauungssäften," Deutsch. med. Wchnschr., 1884, x, 309–310.
Frerichs, E. F. T.: Beiträge zur Lehre von der Tuberkulose, Marburg, 1882, pp. 95–98.
Frommer, I.: "Fälle von aphthösem und von primärem tuberculösem Magengeschwür," Pest. med.-chir. Presse, 1902, xxxviii, 1099–1104.
Fujii, T.: "Beitrag zur Kenntnis der Tuberkulose des Magens," Inaug. Dissert., Göttingen, 1909.
Gaillard: "Tuberculose miliaire simulant au début la fièvre typhoïde. Adénites suppurées multiples. Perforations stomacales et gastrorragies," France méd., 1880, no. 49, p. 361. Cited by Arloing, loc. cit.
Gelpke: Cited by Zesas, loc. cit., p. 471.
Glaubitt: "Über Magentuberkulose," Inaug. Dissert., Kiel, 1901.
Godart-Danhieux: "Sténose pylorique due à un péritonite tuberculeuse," Policlinique, November 1, 1904, p. 481. Cited by Ricard and Chevrier, loc. cit., ii, 105.
"Tuberculose péritoneale simulant un cancer de l'estomac," Policlinique, 1901, p. 183. Cited by Ricard and Chevrier, loc. cit., ii, p. 104.
Gossmann, J. R.: "Ueber das tuberkulöse Magengeschwür," Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxvi, 771–805.
Habershon, S. H.: "Case of Tubercular Ulcer of the Stomach Associated with Tubercular Disease of Pericardium and Other Serous Membranes, and with Multiple Tubercular Tumors of the Brain," Tr. Path. Soc. London, 1894–5, xlv, 73–78.
Hamilton, H.: "Multiple Tuberculous Ulcers of the Stomach, with a Report of Three Cases," Bull. Johns Hopkins Hosp., 1897, viii, 75–79.
Hanau, A.: "Beiträge zur Lehre von der acuten Miliartuberculose," Virchow's Arch. f. path. Anat., 1887, cviii, 221–238.
Happel and Blumer: "A Case of Pulmonary Tuberculosis Associated with Round Ulcer of the Stomach," Albany Med. Ann., 1898, xix, 594.
Hattute: "Ulcère tuberculeux de l'estomac simulant un ulcère simple ou un cancer," Gaz. d. hôp., 1874, no. 108. Cited by Letorey, loc. cit., pp. 35–37.
Hebb, G.: "Tubercular Ulcer of the Stomach," Westminster Hosp. Rep., 1887, iii, 155–158.
Hecker, R.: "Ueber Tuberculose im Kindes- und Säuglingsalter," München. med. Wchnschr., 1894, xli, 391–394.
Heine, L.: "Ueber multiple Magengeschwüre bei Tuberkulose," Inaug. Dissert., Freiburg, 1899. Cited by Arloing, loc. cit.
Herczel: (Rapporte par Alessandria.) Cited by Leriche and Mouriquand, loc. cit., p. 531.
Holt, E.: Disease of Infancy and Childhood, 1897, p. 337.
Holzmann: "Ueber Magentuberkulose," München. med. Wchnschr., 1909, lvi, 207.
Jacobs: "Sténose du pylore par localisation tuberculeuse, gastroenterostomie, guérison," Progrès méd. belg., October 15, 1900. Cited by Brunner, loc. cit., p. 32.
Kanzow: "Ein Beitrag zur Kenntnis der tuberculösen Magengeschwüre," Inaug. Dissert., München, 1895. Cited by Fujii and de Vecchi, loc. cit.
Keen, W. W.: "Tuberculosis or Carcinoma? of the Stomach; Exploratory Celiotomy; Subsequent Apparently Complete Cure," Ann. Surg., 1897, xxv, 750–758.
Kjianowski: "Propriétés bactéricides du suc gastrique," Centralbl. f. Bacteriol., 1891, x, p. 7. Cited by Arloing, loc. cit.
Klebs, E.: "Über heilende und emulsierende Substanzen aus Tuberkel-Bacillen-Kulturen," Centralbl. f. Bakteriol., 1896, xx, 488. Cited by Dürck and Oberndorfer and Arloing, loc. cit.
Kühl, J.: "Über tuberculöse Magen-Geschwüre," Inaug. Dissert., Kiel, 1889.
Kundrat: In Gerhardt's Handbuch der Kinderkrankheiten, 1880, iv, 443–444.
Kurloff and Wagner: "Action du suc gastrique humain sur les germes des maladies," Centralbl. f. Bakteriol., 1890. Cited by Arloing, loc. cit.
Labadie-Lagrave: Bull. Soc. anat. de Paris, 1870. Cited by Letorey, loc. cit., p. 32.
Lancereaux: Atlas d'anatomie pathologique, 1871, xxi, 24. Cited by Arloing, loc. cit.
Lange: Memorabilien, Heilbronn, 1871, xvi, 53. Cited by Arlong, loc. cit.
Lava, G.: "Ulcera tubercolare primitiva del piloro," Gazz. med. di Torino, 1893, xliv, 915–920; 935–939.
Leriche, R., and Mouriquand, E.: "Les formes chirurgicales de la tuberculose de l'estomac," Rev. de chir., 1909, xxxix, 337–353; 520–559.

Letorey, G.: "Contribution à l'étude des ulcerations tuberculeuses de l'estomac," Thèse de Paris, 1895.

Letulle: "Origine infectieuse de certains ulcères simples de l'estomac et du duodénum," Bull. et mém. Soc. méd. d. hôp. de Paris, 1888, p. 360. Cited by Arloing, loc. cit.

Leven: "Gastrectasia due a une compression du pylore par des ganglions tuberculeux," Bull. et mém. Soc. anat. de Paris, February, 1901, p. 114. Cited by Ricard and Chevrier, loc. cit., ii, 94.

Lipscher: Ungar. med. Presse, 1901, No. 27. Abst. in Zentralbl. f. Chir., 1902, No. 29, p. 419.

Lister, T. D.: "A Specimen of Tubercular Ulceration of the Stomach from a Child," Tr. Path. Soc. London, 1899, pp. 83–85.

Litten: "Ulcus ventriculi tuberculosum," Virchow's Arch. f. path. Anat., 1876, lxvii, 615.

Lorey: "Tuberculose bronchique et pulmonaire, ayant donné lieu à des phénomènes de compression des veines-caves; carie de la troisieme côte; symphyse cardiaque. Ulcérations tuberculeuses de l'estomac, ayant amené la mort par hématémèse," Bull. Soc. anat. de Paris, 1874, p. 586. Cited by Letorey, loc. cit., pp. 33–35.

Louis: Traité de la phthisie, Paris, 1825, p. 70. Cited by Arloing, loc. cit.

Lyle, H. H. M.: "Combined Tuberculosis and Carcinoma of the Stomach, with a Report of a Case Upon Which a Partial Gastrectomy was Performed," Amer. Jour. Med. Sci., 1913, cxlv, 691–697.

Marfan, B. J. A.: "Troubles et lesions gastriques dans la phthisie pulmonaire," Thèse de Paris, 1887.

Margarucci, O.: "Della tubercolosi intestinale e del suo trattamento chirurgico," Policlinico, 1898, v, sez. chir., 75–97; 228–252.

Mathieu: "Tuberculose pulmonaire, tuberculose du péricarde, du foie, des reins, des testicules, des ganglions lymphatiques, du mésentère. Ulcération tuberculeuse de l'estomac," Bull. Soc. anat. de Paris, 1881, 632–661. Cited by Letorey, loc. cit., pp. 54–55.

Mathieu and Rémond: Observation XX (inédite). Cited by Letorey, loc. cit., pp. 61–64.

Mayo-Robson and Moynihan: "Tuberculosis of the Stomach," in their Diseases of the Stomach and their Surgical Treatment, Ed. 2, 1904, pp. 455–458.

Melchior, L.: "Zur Pathologie der Magentuberkulose," Beitr. z. Klin. d. Tuberk., 1913, xxvi. Abst. in München. med. Wchnschr., 1913, lx, 1785.

Merry: Thèse de Paris, 1907, p. 219. Cited by Leriche and Mouriquand, loc. cit., p. 530.

Mouisset and Mouriquand: Lyon méd., 1905. Cited by Leriche and Mouriquand, loc. cit., p. 350.

Müller, O.: "Zur Kenntnis der Kindertuberculose," München. med. Wchnschr., 1889, xxxvi, 875–878; 899–903; 917–920.

Musser, J.: "Tuberculous Ulcer of the Stomach," Philadelphia Hosp. Rep., 1890, i, 117.

Nash, W. G.: Primary Hyperplastic Tuberculosis of the Stomach and Duodenum, Proc. Roy. Soc. Med., London, 1900, iii, Clin. Sect., pp. 40–44.

Nordmann, O.: "Zur Chirurgie der Magengeschwülste (Carcinom, Sarkom, Tuberculose)," Arch. f. klin. Chir., 1904, lxxiii, 574–577.

Oppolzer: "Fall von Kommunikation des Magens mit dem Colon transversum," Wien. med. Presse, 1867, viii, 1230–1232; 1265–1267.

Orth: "Experimentelle Untersuchungen über Fütterungs-Tuberkulose," Virchow's Arch. f. path. Anat., 1879, lxxvii, 217.

Papavoine, M.: "Memoire sur les tubercules," Jour. d. sc. méd., 1830, ii, 93.

Papellier: "Ueber die Combination der Tuberkulose mit dem runden Magengeschwür," Inaug. Dissert., Erlangen, 1854. Cited by Arloing, loc. cit.

Patel: Thèse de Lyon, 1902. Cited by Poncet and Leriche, loc. cit.

Patella: Congrès de la tuberculose, Naples, 1901. Cited by Poncet and Leriche, loc. cit.

Paulicky: Berl. klin. Wchnschr., 1867. Cited by Letorey, loc. cit., pp. 30–31.

Petruschky, J.: "Zur Diagnose und Therapie des primären Ulcus ventriculi tuberculosum," Deutsch. med. Wchnschr., 1899, xxv, 394–395.

Pitt, G. N.: "Esophagus and Stomach with Numerous Ulcers Through Which Caseous Glands Have Burst," Tr. Path. Soc. London, 1888, xxxix, 107.

Plambeck, C.: "Ein Beitrag zur Statistik und Verbreitung der Tuberkulose," Inaug. Dissert., Kiel, 1885.

Poncet, A., and Leriche, R.: Bull. de l'Acad. de méd., 1905, liii, 532–542.

Pozzi: "Ulcération tuberculeuse de l'estomac et de l'intestin chez un phthisique," Bull. Soc. anat. de Paris, 1868, xliii, 386. Cited by Letorey, loc. cit., pp. 31–32.

Przewoski, E.: "Gastritis tuberculosa," Virchow's Arch. f. path. Anat., 1902, clxvii. 424–442.

Quénu: "Troubles gastriques de la tuberculose," Mémoire inédite, 1879 (in Thèse de Marfan, 1887). Cited by Letorey, loc. cit., p. 50.

Reinhold, H.: "Ein Fall von Milztuberkulose mit Verblutung durch den Magen," Inaug. Dissert., Kiel, 1899.

Rémon-Verliac: "Ulcère tuberculeux perforant de l'estomac," Bull. et mém. Soc. med. d. hôp. de. Paris, 1907. Cited by Zesas, loc. cit., p. 469.

Ricard and Chevrier: "De la tuberculose et des stenoses tuberculeuses du pylore," Rev. de Chir., 1905, i, 557, 736; ii, 74.

Rilliet, F. and Barthez, A. C. E.: Traité clinique et pratique des maladies des enfants, Ed. 3, Paris, 1891, Vol. 3, pp. 1260–1271.

Roger: "De la perforation de l'estomac dans la phthisie," Thèse de Paris, 1898. Cited by Arloing, loc. cit.

Rokitansky, C.: Pathological Anatomy, 1855, Vol. 2, p. 43.

Rosset, W.: Über einen Fall von tuberculösen Magengeschwür, mit besonderer Berücksichtigung der Genese, Freiburg, 1903.

Ruge: "Über primäre Magentuberkulose," Beitr. z. Klin. d. Tuberk., 1904–5, iii, 191.

Satterthwaite, T. E.: "Non-malignant Gastric and Duodenal Ulcers with Illustrative Cases," Med. Rec., 1900, lvii, 485–490.

Schede: Cited by Brunner, loc. cit., p. 30.

Schlesinger, H.: "Die Pylorustuberkulose und der tuberkulöse Wandabszess des Magens," München. med. Wchnschr., 1914, lxi, 987–989.

Schoull: "Contagion de la tuberculose par les aliments des tuberculeux," Compt. rend. Cong. tuber., 1891, p. 256. Cited by Arloing, loc. cit.

Serafini, A.: "Contribuzione della casuistica della tuberculosidello stomaco," Ann. clin. Osp. de Napoli, 1888. Cited by Letorey, loc. cit., pp. 56–57.

Sigg, A.: "Beiträge zur Lehre von der acuten Miliartuberculose," Inaug. Dissert., Zurich, 1896.

Simmonds, M.: "Ueber Tuberculose des Magens," München. med. Wchnschr., 1900, xlvii, 317–318.

Sokolowski: Ueber die larvirten Formen der Lungentuberkulose, Wien, Braumüller, 1890. Cited by Arloing, loc. cit.

Sormani: Rendicanti del R. Instituto Tomb., fasc. 10, 1884. Cited by Arloing, loc. cit.

Steiner und Neureutter: "Paediatrische Mittheilungen," Prag. Vierteljahrschr., 1865, ii, 34–58.

Stelter, F.: "Über die tuberkulösen Geschwüre des Magens," Inaug. Dissert., Greifswald, 1902.

Still, G. F.: "Tubercular Ulcer of the Stomach in Children," Tr. Path. Soc. London, 1899, pp. 76–83.

Straus and Würtz: "Action du suc gastrique sur quelques microbes pathogenes," Arch. de méd. expér. et d'anat. path., 1889, p. 370. Cited by Arloing, loc. cit.

Struppler, T.: "Über das tuberkulöse Magengeschwür im Anschluss an einen Fall von chronisch-ulceröser Magentuberkulose mit tödlicher Perforationsperitonitis," Ztschr. f. Tuberk. u. Heilstättenw., 1900–1, i, 206–209; 311–316.

Talamon, C.: "Phthisie locale; ulcérations tuberculeuses de l'estomac et de l'intestin; carreau," Progrès méd., 1879, vii, 46–48.

Thorel: Festschrift des neuen Krankenhauses in Nürnberg, 1898. Cited by Arloing, loc. cit.

Tichoff: (Résumé.) Chirurgie, June, 1908, pp. 632–640. Cited by Leriche and Mouriquand, loc. cit., p. 531.

Toulmouche: "Des ulcères de l'estomac," Arch. gén. de méd., 1869, xiv, ii, 272, 385, 555. Cited by Arloing, loc. cit.

Tripier, R.: "Des gastrorrhagies dans leur rapport avec les ulcérations stomacales et de leur traitement par les lavements d'eau chaude," Semaine méd., 1898, xviii, 241–245. Cited by Arloing, loc. cit.

Vallas: Tuberculose hypertrophique de l'estomac. Résection; duodenostomie; anastomose cardio-jéjunale secondaire; mort. Cited by Leriche and Mouriquand, loc. cit.

Van Wart, R. M.: "Solitary Tubercle of the Stomach," Bull. Johns Hopkins Hosp., 1903, xiv, 235–237.

Virchow: Cited by Stelter, loc. cit.

Von Tappeiner, H.: "Beitrag zur Kenntnis der tuberkulösen Pylorus stenose," Beitr. z. klin. Chir., 1910, lxvi, 371–376.

Weinberg: "Ulcère gastrique tuberculeux chez une jeune fille de douze ans avec tuberculose généralisée," Bull. Soc. anat. de Paris, 1896, p. 408. Cited by Arloing, loc. cit.

Wesener: Beiträge zur Lehre von der Fütterungstuberkulose, Freiburg in Brisgau, 1885, pp. 55–60. Cited by Arloing, loc. cit.

Widerhofer, H.: "Die Krankheiten des Magens und Darms," Gerhardt's Handbuch der Kinderkrankheiten, 1880, iv, 341–664.

Wilms, M.: "Miliartuberculose des Magens," Centralbl. f. allg. Pathol. u. path. Anat., 1897, viii, 783–789.

Winternitz, M. C.: "Tuberculosis of the Stomach; Tuberculous Cavities of the Liver with Report of a Case," Bull. Johns Hopkins Hosp., 1908, xix, 223–228.

Zagari, G.: "Sul passaggio del virus tubercolare pel tubo digerente del cane," Gior. internaz. d. sc. med., 1889, n. s. xi, 641–674. Cited by Arloing, loc. cit.

Zesas, D. G.: "Die Tuberkulose des Magens," Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1913, xvi, 448–508.

THE PATHOLOGIC REASONS FOR THE LEGITIMATE ERROR IN X-RAY DIAGNOSIS OF GASTRIC CARCINOMA AND ULCER *

WILLIAM CARPENTER MacCARTY

An analysis of the pathologic conditions in the stomach in relation to the physical basis of roentgenology necessitates a consideration of two things, i. e., the physical facts which make the roentgen rays capable of utilization and the anatomicopathologic facts relative to gastric lesions.

As utilized in the diagnosis of gastric carcinoma and gastric ulcer, roentgenology depends upon structural abnormality, abnormality of gastric rhythm, tissue density, and the behavior of artificially administered dense gastric contents.

From a standpoint of the pathology of these two conditions experience with 862 specimens which were removed by excision or resection at operation distinctly shows that there are no recognizable differences in structural outlines in early carcinoma and simple chronic ulcers (Figs. 110–120). The ulcerations in both conditions may be deep or shallow, large or small, and may possess overhanging, gradually receding, hypertrophic or atrophic borders (Figs. 114–117 and Fig. 129). The specimens themselves, in the hands of a most competent surgical pathologist, cannot be positively differentiated from their outlines.

In regard to functional rhythm, with which roentgenologists have had more experience than the writer, it might be said, from the anatomic basis of rhythm which lies in the contractility and continuity of the musculature, that there is nothing characteristic in either simple gastric ulcer or carcinomatous gastric ulcer. In both conditions the musculature may be intact or broken and histologically normal or abnormal.

The behavior of dense gastric contents as an aid to x-ray diagnosis

is valuable only in that it aids in the recognition of structural abnormality
and the character of gastric rhythm and therefore may be considered
merely a tool to be utilized in the study of these two factors.

Tissue density from an *x*-ray standpoint is a field for investigation
which has been scarcely touched in the literature. That large amounts
of carcinomatous tissue may have a recognizable difference in density
from purely inflammatory or normal tissue is highly conceivable, but that

Fig. 110.—(C A76,248.)   Gastric carcinoma.

quantity of tissue examined plays an enormous rôle in the *x*-ray deter-
minations of density is likewise conceivable.

To the pathologist the essential feature of the question as to the
roentgenologist's ability to diagnose gastric carcinoma from simple
chronic ulcer is one simply of the quantity of carcinomatous tissue which
is recognizable by means of the *x*-rays. I shall, therefore, merely state
the anatomicopathologic facts which have been determined from a study
of 318 chronic gastric ulcers and 602 carcinomatous chronic gastric ulcers.

1. There are conditions of advanced carcinoma associated with gas-

'16—14

tric ulceration in which there is no possibility of determining which condition was primary (Fig. 115).

2. There are simple chronic gastric ulcers in which there are no visible signs of carcinoma (Figs. 112, 113, 114, 116, 118).

3. There are simple chronic gastric ulcers in which the epithelium of the gastric tubules is intact, the cells being columnar or cuboid and regularly arranged; the interglandular stroma is infiltrated with lympho-

Fig. 111.—(C A68,087.)   Gastric ulcer.

cytes and there are congestion and edema coincident to chronic inflammatory reaction in the mucosa (Figs. 121, 122, 123). This condition of the epithelium has been described by the writer as primary epithelial cytoplasia.

4. There are simple chronic gastric ulcers which are indistinguishable in every anatomic and histologic detail from ulcers which have just been described except the condition of a part or all of the glandular epithelium. In this group the intratubular, columnar, or cuboid cells are to-

tally or partially replaced by irregularly arranged ovoid or spheroid cells which have clear protoplasm, centrally placed, and less dense nuclei with prominent nucleoli. It has been repeatedly observed that these spheroid

Fig. 112.—(H 18,088.)   Multiple simple ulcers and one large carcinomatous ulcer.

Fig. 113.—(H 28,173.)   Simple gastric ulcer.

or ovoid cells are morphologically indistinguishable from unquestioned carcinomatous cells which are found in the stroma and metastases. This condition has been described as secondary epithelial cytoplasia (Fig. 126).

Fig. 114.—(C A43,484.) Simple gastric ulcer.

Fig. 115.—(H 21,882.) Deep gastric carcinoma.

Fig. 116.—(H 18,088.) Cross-section through Fig. 112

Fig. 117.—(C A76,248.) Cross-section through Fig. 110.

Fig. 118.—(H 28,173.) Cross-section through Fig. 113.

Fig. 119.—(H 21,555.) Cross-section through an early car-
cinomatous ulcer.

5. There are chronic gastric ulcers similar in all histologic charac-teristics to the ulcers just described plus the presence of the ovoid or spheroid cells in the interglandular stroma, the line of demarcation between the tubules and the stroma being confused or absent, a condi-tion described as tertiary or migratory cytoplasia (Figs. 127, 128). Pri-mary epithelial cytoplasia is a benign cellular condition; secondary epithelial cytoplasia is a cellular precancerous condition, and tertiary or

Fig. 120.—(C A68,087.) Cross-section through Fig. 111.
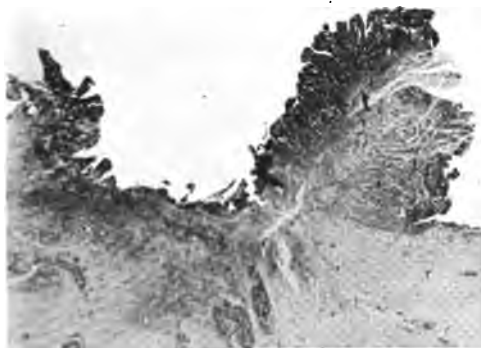
Fig 121.—(C A86,829.) Simple chronic ulcer.

migratory epithelial cytoplasia is a definitely malignant condition (Figs. 123, 126, 128, and 130).

These facts in the gastric mucosa are in accord with cytologic facts regarding certain tissues in other organs which have served to form the basis of a modern biologic conception of cancer. It has been repeatedly stated by the writer that cancer is a migratory hyperplasia of the regen-erative cells of a tissue, a generalization which has for its basis a biologic study of cells in general and the facts observed in the attempted regen-eration of tissues after destruction, during which regeneration there is

hypertrophy, hyperplasia and finally migration of the cells that normally regenerate the specific cells characterizing or constituting a tissue.

Without entering into a prolonged exposition of this phase of the
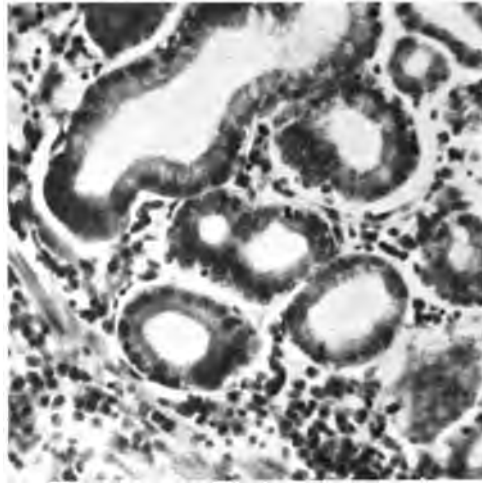
Fig. 122.—(C A73,003.)
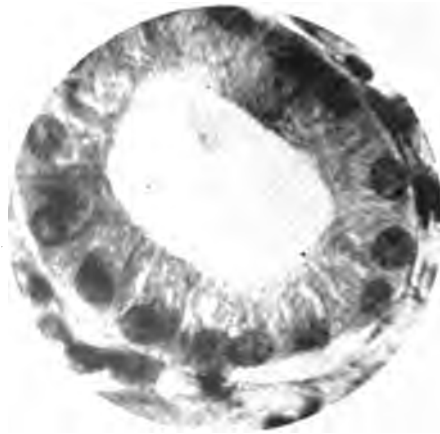
Fig. 123.—(C A75,082.)

Figs. 122 and 123.—Epithelial conditions in simple chronic gastric ulcers.

subject it is sufficient to say that carcinoma as well as all forms of neoplasia is a question of cells, the earliest recognizable changes in which are only visible under the highest powers of the microscope. This being

a fact, it is not conceivable that the roentgenologist, the clinician, and the surgeon will ever be able to differentiate a simple chronic gastric ulcer from a simple chronic gastric ulcer with early carcinomatous changes,
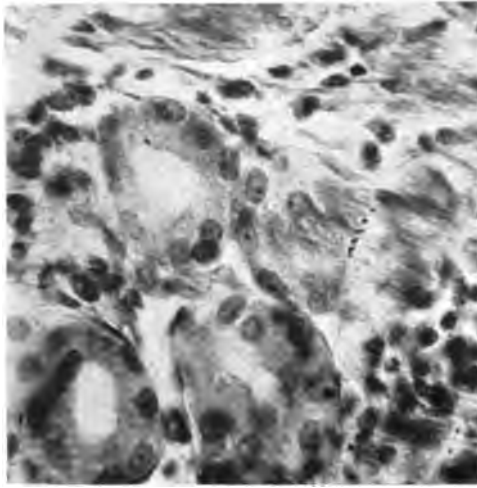
Fig. 124.—(C A84,970.)

Fig. 125.—(C A75,082.)

Figs. 124 and 125.—Epithelial conditions in simple chronic gastric ulcers.

the latter condition being, as experience has taught us, the only pathologic condition in the stomach in which a malignant neoplasia can possibly be completely cured with any known therapeutic agents.

It is certainly true that the roentgenologist, the clinician, and the surgeon can recognize advanced carcinoma, but the assumption that a

Fig. 126.—(C A55,230.) Secondary epithelial cytoplasia in the border of a gastric ulcer.

Fig. 127.—(C A84,970.) Tertiary or migratory epithelial cytoplasia in the border of a gastric ulcer.

few distinctly carcinomatous migratory cells within the confines of the mucosa will alter the physical conditions, which are the basis of x-ray diagnosis, so as to prove malignancy, seems inconceivable to the surgical

pathologist who must search with a microscope before making the diagnosis.

There is no further need to attempt to demonstrate the impossibility of gross differential diagnosis because every honest clinician, roentgenologist or surgeon who has had any extensive experience with gastric conditions has made diagnoses of gastric carcinomas which were simple chronic ulcers and diagnoses of simple chronic ulcers which were carcinomas; indeed, they have even made diagnoses of these conditions without finding any demonstrable gastric lesion. It is not my duty as a pathologist to analyze, for presentation, a large itemized series of mistakes in the *x*-ray diagnosis between the conditions under discussion. This should be left

Fig. 128.—(C A84,970.) Tertiary or migratory epithelial cytoplasia in the border of a gastric ulcer.

for the scientific roentgenologist who, by so doing, might keep less experienced roentgenologists from deceiving themselves and assist them toward a higher and more scientific conception of medical efficiency.

There is another bit of individually known evidence which has evolved in the experience of those who have to do with gastric conditions from an *x*-ray standpoint; the terms "gastric," "pyloric," and "prepyloric" lesion have come prominently to the front. This fact simply means that the roentgenologists, like other clinicians, are beginning to experience what was known centuries ago to a Chinese physician, who wrote a work on medicine in which he stated that the successful physician is the one who recognizes the possible from the impossible.

It is certainly true that the roentgenologist, the clinician, and the surgeon can recognize advanced carcinoma, but the assumption that a

Fig. 126.—(C A55,230.) Secondary epithelial cytoplasia in the border of a gastric ulcer.

Fig. 127.—(C A84,970.) Tertiary or migratory epithelial cytoplasia in the border of a gastric ulcer.

few distinctly carcinomatous migratory cells within the confines of the mucosa will alter the physical conditions, which are the basis of x-ray diagnosis, so as to prove malignancy, seems inconceivable to the surgical

pathologist who must search with a microscope before making the diagnosis.

There is no further need to attempt to demonstrate the impossibility of gross differential diagnosis because every honest clinician, roentgenologist or surgeon who has had any extensive experience with gastric conditions has made diagnoses of gastric carcinomas which were simple chronic ulcers and diagnoses of simple chronic ulcers which were carcinomas; indeed, they have even made diagnoses of these conditions without finding any demonstrable gastric lesion. It is not my duty as a pathologist to analyze, for presentation, a large itemized series of mistakes in the *x*-ray diagnosis between the conditions under discussion. This should be left

Fig. 128.—(C A84,970.) Tertiary or migratory epithelial cytoplasia in the border of a gastric ulcer.

for the scientific roentgenologist who, by so doing, might keep less experienced roentgenologists from deceiving themselves and assist them toward a higher and more scientific conception of medical efficiency.

There is another bit of individually known evidence which has evolved in the experience of those who have to do with gastric conditions from an *x*-ray standpoint; the terms "gastric," "pyloric," and "prepyloric" lesion have come prominently to the front. This fact simply means that the roentgenologists, like other clinicians, are beginning to experience what was known centuries ago to a Chinese physician, who wrote a work on medicine in which he stated that the successful physician is the one who recognizes the possible from the impossible.

MODEL OF GASTRIC TUBULES IN EARLY GASTRIC CANCER *

LOUIS B. WILSON

In the study of early gastric cancer in relation to gastric ulcer, I have previously reported† what appear to me to be segregated masses of gastric mucosa cut off from the surface by necrosis and subsequent formation of scar tissue, and yet containing living epithelial cells apparently capable of functionating. Some doubt might well exist as to whether these were not misinterpretations of oblique sections. I long ago satisfied myself that this was not true by following throughout such isolated portions of tubules in serial sections. Of several such specimens I made photographs, and of others drawings with the camera lucida, covering the entire series. Last summer Mr. James A. Wynn reconstructed from the drawings of one such series a model, the photograph of which is herewith shown (Fig. 131).

This reconstruction was made from drawings of sections through the edge of a large chronic gastric ulcer in one small area, on the opposite side of which there was unmistakable evidence of beginning cancer. The tubules bore the same relation to the normal surface of the mucosa that they here bear to the surface of the upper side of the case surrounding the model. It will be observed that a number of them have been completely reconstructed and that they do not communicate with the surface. Some of the smaller ones contain atrophic epithelium. The larger ones are very much larger than the ends of other gastric tubules from a nearby normal region reconstructed on the same scale, and shown in the photograph. The epithelium of the dilated tubules was much swollen. Some of the tubules were cystic and filled with mucus.

Since the segregated glandular masses contained epithelium capable of functionating and still connected with their nerve and blood supplies, their possible relationship in cases of gastric ulcer to the pain occurring
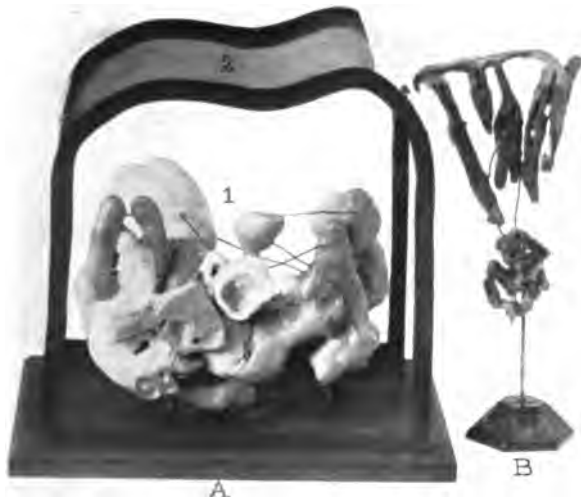
Fig. 131.—*A*, Reconstruction of group of portions of gastric tubules segregated in border of gastric ulcer; *1* tubules; *2*, surface of cover representing base of ulcer. *B*, Group of normal tubules from neighboring region in same specimen—same magnification as *A*.

during digestion is suggested. Food in the stomach may cause the same sort of pain in these areas as is present in the parotid gland when a patient with mumps eats sour foods.

THE ETIOLOGY OF CHOLECYSTITIS AND GALL-STONES AND THEIR PRODUCTION BY THE INTRAVENOUS INJECTION OF BACTERIA *

EDWARD C. ROSENOW

— ——

The lodgment and growth of bacteria in the gallbladder have been considered chiefly as accidental, notwithstanding the fact that bacteriemia occurs in numerous diseases in which cholecystitis is absent. Attempts by investigators to produce cholecystitis by simple intravenous injection of various bacteria have usually resulted in failure. The typhoid bacillus, however, quite irrespective of its source, has given positive results in the hands of Blachstein,[1] Welch,[2] Cushing,[3] Koch,[4] Gay and Claypole,[5] and Nichols.[6]

During the course of experiments[7] with laboratory strains of streptococci I noted that lesions of the gallbladder followed intravenous injection of these strains only when the virulence had attained a certain point. Two years ago I reported a case[8] in which cholecystitis had occurred ten days after tonsillitis, and in which a streptococcus had been isolated from the wall of the gallbladder and from the centers of the newly formed gall-stones. This streptococcus had shown a far greater affinity for the gallbladder. in animals than had streptococci from other diseases.[9]

In this paper I wish to record the results of cultures by special methods from the liquid contents of the gallbladder, from the centers of gall-stones, from the wall of the gallbladder, and from the adjoining lymph-glands removed at operation, in a series of cases of cholecystitis, and the results of animal experiments with the bacteria thus isolated. These results, it is believed, throw definite light on the mechanism of the occurrence of cholecystitis and gall-stones.

TECHNIC

The gallbladder or adjacent lymph-glands were removed aseptically with as little exposure to the air and skin as possible, covered at once

with sterile gauze, and taken unopened to the laboratory. The contents were collected in pipets; a portion of the gallbladder (0.5 cm. by 1 cm.) was excised, and one or more stones, if present, were saved for cultures. The pieces of tissue from the gallbladder and the lymph-glands were washed twice in salt solution, the surfaces flamed or seared with a blade, and then the tissue emulsified in a mortar in a specially devised sterile air chamber.[10]

Cultures from the gall-stones were made from pulverized material taken from the centers by means of a small dental burr, after the surfaces had been seared with a blade. Control cultures from more superficial portions were made in some instances. The cultures were made in tall columns of liquefied ascites (10 per cent.) dextrose (1 per cent.) agar, in ascites-dextrose broth, in litmus milk, and on blood-agar slants. In some instances pieces of sterile tissue, guinea-pig heart or kidney, were added to the bottom of the shake cultures in agar. The cultures were incubated at from 35° to 37° C. for at least ten days before being discarded, and were examined daily.

The bacteria for injection were usually from single colonies in the shake cultures, and had been grown in tall columns (12 cm.) of ascites-dextrose broth containing sterile tissue, for from eighteen to twenty-eight hours, centrifugalized, the clear broth poured off, and the bacteria suspended in salt solution so that 1 c.c. contained the growth from 15 c.c. of the broth culture. The injections were made intravenously through a 23-gage needle with a glass syringe, sterilized by boiling. The portion of the suspension left over was preserved in the ice-chest for further injections in case the results warranted further study. This method was found to preserve the elective property of the bacteria in the presence of pieces of sterile tissue for a longer time than repeated subcultures. In one instance it endured for as long as twenty months (Case 140). Blood-agar-plate cultures and smears were made from the suspensions at the time of the injections to prove the viability of the organisms at the time of injection and to be used in the study of cultural features. In most experiments the injections were made some hours after the feeding period. The dogs were fed meat and bread or dog biscuits, the rabbits and guinea-pigs liberal amounts of greens, bread, or oats and hay.

The necropsies were made as soon after death as possible. A careful inspection in a bright light, aided with a hand lens, was made for focal lesions. Cultures were made routinely from blood, bile, joint fluid, and the emulsified tissues of the wall of the gallbladder. The pieces of tissue saved for microscopic study were fixed in Kaiserling's solution, Zenker's solution, 10 per cent. formalin, or in 80 per cent. alcohol.

RESULTS OF THE CULTURES IN HUMAN CHOLECYSTITIS

Of the patients in whom sex was noted, 25 were females and 13 males. The youngest was eighteen years of age, the oldest, sixty-eight. There

were 28 between the ages of thirty and sixty years. The duration of symptoms in the different cases ranged between six weeks and twenty-five years.

The cultures were made from material removed at operation in 47 cases. The bile or other fluid content of the gallbladder (Table 1) was cultured in 29 cases, 13 of which showed no bacteria. In the remaining 16 cases the streptococcus was not found in pure culture, being associated with the colon bacillus in 5 instances, and with other bacteria in 2. The colon bacillus was found in pure culture 4 times.

Cultures from the nuclei of the common types of gall-stones were made in 33 cases and showed no bacteria. In the remaining 29 cases the streptococcus was isolated in pure culture in 17, and the colon bacillus in pure growth in 1. The streptococcus occurred with the colon bacillus in 3 cases, and with other bacteria in 4. Cultures made from 4 typical cholesterol stones (not given in tables) showed no streptococci; 2 were sterile; 1 yielded a few colonies of a diphtheroid bacillus; and 1 yielded the colon bacillus.

Cultures from the wall of the gallbladder were made in 32 cases, 5 of which were sterile. Of the remaining 27, the streptococcus was found in pure culture in 10, the colon bacillus in 1, mixtures of streptococcus and colon bacillus in 8, and the streptococcus with other bacteria in 3.

Of the cases in which the fluid contents were sterile, the streptococcus was isolated from the wall of the gallbladder in 8, and from the center of gall-stones in 6.

The adjacent lymph-glands were cultured in 8 cases; 1 gave no bacteria, 4 showed pure cultures of the streptococcus, 1 the streptococcus and a diphtheroid bacillus, and 1 a pure culture of colon bacillus.

Bacillus welchii was found in conjunction with other bacteria in the gall-stones in 7 cases, and in the wall of the gallbladder and in the adjacent lymph-glands in 1 instance each. It was not obtained in cultures from the fluid contents. Staphylococcus aureus alone was present in the contents and wall in 1 case, and in mixture with the colon bacillus in 1 case of acute cholecystitis. Diphtheroid bacilli were found pure in the gallbladder wall in 1 case, and in mixture with streptococci in the contents in 1, in the wall in 2, and in a lymph-gland in 1. Fusiform bacilli were found in conjunction with the colon bacillus or the streptococcus in the contents and in the wall in 2 cases. Bacillus mucosus was found in conjunction with Staphylococcus aureus in the contents in 1 case, and

in conjunction with the colon bacillus and the fusiform bacillus in the wall of the gallbladder in 1 case, both in acute cholecystitis. Unidentified strictly aërobic bacilli and cocci, which were found occasionally, were considered contaminations. The typhoid bacillus was isolated from the center of a gall-stone in 1 case.

The cultures from the outer portion of the gall-stones were sterile when the fluid contents were sterile, and contained a bacterial flora similar to that found in the fluid contents when the latter were infected. The nuclei of the stones, on the other hand, often yielded pure cultures of streptococci, irrespective of the bacterial flora of the fluid contents. In 12 cases the streptococcus was isolated both from the center of the stone and from the wall of the gallbladder. In 5 cases of advanced chronic cholecystitis without stones, streptococci were isolated from the wall of the gallbladder. In 5 cases of chronic catarrhal cholecystitis without stones, in which the changes were slight, streptococci were isolated in 1, a few colon bacilli in 2, and no bacteria in 2. In 5 cases of chronic catarrhal cholecystitis with stones the streptococcus was isolated from the center of the stones in 2 cases, and a diphtheroid bacillus in 1. In 9 cases of acute cholecystitis in the first attack or during an acute exacerbation of a chronic cholecystitis, cultures showed the streptococcus alone or in combination with other bacteria in the wall in 7 cases, and in the stones in 5; the colon bacillus was found in 4 of these, Bacillus mucosus in 2, and the staphylococcus in 2. Streptococci were found in small numbers either in the stone or in the wall of the gallbladder in 4 cases in which the mucous membrane of the gallbladder presented the so-called strawberry appearance.[11]

The gross and microscopic changes in the gallbladders studied were of the usual character. Those in which there were chronic changes, and which had been removed during the quiescent interval, showed fibrosis with little cellular infiltration, while those in which there had been a recent acute attack had hemorrhages and marked infiltration, chiefly in the submucosa and subperitoneal coat. Cross-sections at the apex of the gallbladder revealed no noteworthy changes in the nerve-trunks. The eosinophilic infiltration of the fibrous tissue was often a striking picture. The bacteria were found in the areas of hemorrhage and infiltration in relatively large numbers, but were demonstrated also in the more or less dense fibrous tissue in the gallbladders with chronic changes only.

REVIEW OF IMPORTANT CASES AND ANIMAL EXPERIMENTS

CASE 61.—A woman, fifty-nine years of age, who had suffered for fifteen years from symptoms referable to the gallbladder or the stomach, was operated on during an exacerbation of symptoms, August 11, 1914.

Fig. 132.—Chain of streptococci and Bacillus welchii, causing infiltration in the gallbladder. Case 61. Gram-Weigert (× 1200).

The gallbladder, full of stones, and a gland the size of a navy-bean at the juncture of the cystic and common ducts, were removed. A rather large indurated ulcer was also found at the lesser curvature of the stomach. Cultures were made from a portion of the gallbladder wall, 0.5 cm. square, showing what appeared to be an infarcted area, and from the bile, the lymph-gland, and the centers of two of the stones.

August 12: Tall tubes of ascites-dextrose and dextrose agar inoculated with the emulsion of the wall yielded altogether 28 colonies of streptococci, while those inoculated with the emulsion of the gland gave 5. All the colonies were in the upper three-fourths of the tubes. In one tube inoculated with a large amount of the emulsion of the gallbladder wall there were 2 colonies of B. welchii. The centers of the gall-stones yielded a short-chained streptococcus in dextrose broth. The cultures from the bile remained sterile. Subcultures were made on blood-agar plates from 6 of the colonies from the wall of the gallbladder, from 2 from the gland, and from the growth in the broth inoculated with material from the centers of the stones. The rest of the colonies were not disturbed.

August 13: Blood-agar plates showed small, grayish-green, moist, but discrete, quite opaque colonies of short-chained streptococci in pure culture.

August 25: Subcultures from original colonies, which had grown to be 2 mm. in diameter, were made, by means of small pipets, into the usual flasks of ascites-dextrose broth containing sterile tissue.

Fig. 133.—Photograph of the material found in the hemorrhagic and infiltrated gallbladder of Dog 158 after repeated intravenous injections of streptococci. Black gall-stones are embedded in the flakes of mucopurulent material (natural size).

August 26: The broth showed a dense, diffuse turbidity with slight sediment and marked acidity. After centrifugalization, the supernatant broth was poured off, and the sediment suspended in NaCl solution to be injected into animals.

Sections through the infarcted area near the fundus showed leuko-

cytic infiltration, and easily findable streptococci and B. welchii (Fig. 132). Cross-sections at the apex of the gallbladder, near the juncture of the cystic duct, showed fibrosis of the interstitial tissue, thickening of the walls of the blood-vessels, with moderate leukocytic and round-cell infiltration around blood-vessels in the interstitial tissue and submucosa. A few diplococci were found in the areas of leukocytic infiltration. In the interstitial tissue leukocytes were chiefly eosinophils. Nerve-trunks and the mucous membrane were quite free from changes.

Intravenous injection into 1 dog and 1 rabbit of the streptococcus from the gland produced localized hemorrhages and edema in the gall-bladders of both, while the streptococcus from the wall of the gallbladder, as isolated, produced cholecystitis in 2 dogs injected, as well as in 2 dogs after 1 animal passage. Two of 3 rabbits developed no lesions in the gallbladder; the other had cholecystitis. In 1 rabbit and 2 of the dogs with cholecystitis were numerous small black gall-stones imbedded in a thick black mucus containing bile (Fig. 133). The opening in the ampulla of Vater in the rabbit was plugged with a similar material. This is interesting because the gallbladder from which the strain was isolated was filled with stones proved to contain streptococci.

RABBIT 794.—Injected intravenously, August 26, with the growth from 45 c.c. of an ascites-dextrose-tissue broth culture of the streptococcus isolated from the gland.

August 28: Rabbit seemed well. Killed. Gallbladder distended with thick, greenish-black bile, in which were a large number of black particles from 0.5 to 1.5 mm. in diameter. Ducts dilated; bile not to be expressed until the plug of mucus containing soft stones was removed from the ampulla. Wall of the gallbladder thickened and edematous. Few small hemorrhages at the base of the tricuspid valve and in the lung. Joint fluid slightly turbid.

August 29: Liver, blood, and bile cultures sterile.

DOG 105.—Injected intravenously, August 26, with the growth from 90 c.c. of an ascites-dextrose-tissue broth culture of the streptococcus from the wall of the gallbladder.

August 29: The animal seemed well. Chloroformed. No noteworthy lesions anywhere except a marked hemorrhagic cholecystitis. Gallbladder wall edematous and hemorrhagic, particularly at the apex; from 0.3 to 0.6 cm. in thickness. Mucous membrane edematous, in places ulcerated and separated from the serous coat by marked hemorrhage; covered with thick, adherent, bile-stained mucus. A number of small hemorrhages along the cystic duct, but none along the common and hepatic ducts. Joint fluid clear.

August 31: Cultures in blood agar from the bile, blood, liver, and joint fluid were sterile, while those from the wall yielded a pure growth of streptococci in ascites-dextrose agar and broth, and on blood-agar

plates. Sections of the gallbladder showed marked hemorrhage in the subperitoneal layer and moderate leukocytic infiltration. This was most marked in the submucosa and in the peritoneal coat, where a moderate number of Gram-positive diplococci were found.

CASE 85.—A man, sixty years of age, who had not been ill until after a misstep from a ladder five months previous to examination. Since then he had had pain in the epigastrium, dizziness, and for a time chills and fever. At operation on August 15, 1914, there were disclosed a distended and somewhat thickened gallbladder, marked pancreatitis of the head of the pancreas, and enlarged lymph-glands along the cystic and common ducts. The gallbladder contained a large amount of dark bile and masses of tenacious mucus, in which were embedded a very large number of black particles, biliary sand, varying in size from that of a pin-point to that of a grain of wheat. In smears from the bile and from the centers of the stones was what appeared to be B. fusiformis. In cultures from the bile, from the centers of two of the stones, and from the wall of the gallbladder there were streptococci and colon bacilli. The organism resembling B. fusiformis which was found in smears failed to grow. Two dogs and one rabbit injected intravenously with the streptococcus soon after isolation developed cholecystitis. In the two dogs in which injections were made into the portal vein, there were no lesions of the gallbladder or of other organs. The two dogs in which the general circulation had been injected had mild arthritis in addition to the cholecystitis, and one had hemorrhage of the stomach.

DOG 107.—Injected August 26, in the leg vein, with the growth from 60 c.c. of an ascites-dextrose-tissue broth culture of the streptococcus from the gallbladder wall in the shake cultures in ascites-dextrose agar.

August 28: Seemed well. Chloroformed. Three circumscribed hemorrhages in the mucous membrane of the gallbladder and one in the mucous membrane of the lesser curvature of the stomach.

August 29: Cultures from blood, joint fluid, and bile were sterile on blood agar, but those from the blood in dextrose broth gave short-chained streptococci.

DOG 113.—On August 26 a small radicle of the portal vein was injected with the growth from 60 c.c. of an ascites-dextrose broth culture of the streptococcus as isolated from the gallbladder wall.

August 29: Seemed well. Chloroformed. A localized peritonitis and plastic adhesions at the point of injection. In the gallbladder and elsewhere, no changes.

August 31: Cultures on blood agar of joint fluid, blood, liver, and bile were sterile, while the broth culture of the bile yielded a pure growth of a short-chained streptococcus.

CASE 120.—A man, fifty-five years of age, suffering with chronic cholecystitis and chronic duodenal ulcer was operated on August 20,

1914. There were found a gallbladder with marked sclerosis and thickening, a large indurated ulcer of the duodenum just outside the pylorus, adherent to the head of the pancreas, and a pea-sized lymph-gland draining the ulcer. The gallbladder, containing bile and one stone 2 cm. in diameter, and the gland were removed and cultured.

Cross-sections of the apex of the gallbladder revealed marked fibrosis of the submucous muscularis and peritoneal coat, thickening of the blood-vessels, hemorrhagic infiltration, chiefly of the peritoneum and subperitoneum, atrophy of the mucous membrane, and a few diplococci in the hemorrhagic areas.

Cultures from the bile were negative. In the center of the stone were streptococci, colon bacilli, and B. welchii. The gallbladder wall and the lymph-gland draining the ulcer yielded pure cultures of the streptococcus. These strains were similar in appearance, but those from the lymph-gland produced long chains and colonies with a distinct green zone on blood-agar plates, while those from the ulcer produced grayish colonies with no tinge of green.

The streptococcus from the gallbladder wall produced cholecystitis in two dogs injected, but no other noteworthy lesions, while the streptococcus from the lymph-gland draining the ulcer produced hemorrhage and ulcer of the stomach in one of two dogs and in both of two rabbits. The dog without lesions in the stomach or duodenum showed no other lesions. One rabbit, in addition to ulcer, had mild arthritis and a few hemorrhages in the subcutaneous tissue and muscles.

DOG 114.—Injected intravenously, August 28, with the growth from 30 c.c. of an ascites-dextrose broth culture of the streptococcus isolated from the wall of the gallbladder.

August 31: Seemed well. Chloroformed. A number of small hemorrhages from 0.3 to 0.8 cm. in diameter and edema of the gallbladder, especially along its attachment to the liver. No changes in bile-ducts, appendix, stomach, duodenum, or pancreas.

September 1: Blood-agar plate cultures from the bile gave 6 colonies of streptococci, and cultures from the gallbladder wall yielded 3 colonies of streptococci and 4 colonies of colon bacilli. Blood and joint fluid sterile.

DOG 109.—Injected intravenously, August 26, with the growth from 120 c.c. of an ascites-dextrose broth culture of the streptococcus isolated from the gland draining the ulcer.

August 28: Seemed well. Chloroformed. No gross lesions except numerous small punctate hemorrhages scattered over three circumscribed areas in the pyloric ring. In the centers of two of these the mucous membrane was necrotic and ulcerated.

RABBIT 700.—Injected intravenously, August 26, with the growth from 15 c.c. of an ascites-dextrose broth culture of the streptococcus isolated from the gland draining the ulcer.

August 28: Killed. No gross lesions except ulcer, 0.2 cm. by 0.4 cm., at the juncture of the middle and lower thirds of the stomach, near the lesser curvature. Base hemorrhagic; mucous membrane ulcerated and undermined.

August 29: Cultures from blood, joint fluid, and bile were negative, while the culture from the ulcer yielded approximately 100 colonies of streptococci.

CASE 135.—A woman, sixty-eight years of age, with chronic chole-cystitis and an acute exacerbation. The attack of cholecystitis with chills and fever had begun ten days previously. Symptoms of stones in the gallbladder dated back fifteen years. The patient had never been jaundiced. At operation, August 22, 1914, there were disclosed a greatly thickened gallbladder containing many stones and mucopurulent ma-terial free from bile, an inflamed and dilated common duct, the size of the small intestine, containing one large stone, and enlarged lymph-glands along the cystic and common ducts. The gallbladder and one lymph-gland were removed and cultures made.

August 23: In the cultures from the centers of two of the stones, from the wall of the gallbladder, and from the mucopurulent material, were streptococci and colon bacilli, while in those from the gland there were streptococci only. There were more colonies of colon bacilli than of streptococci from the mucopus and from the centers of the stones, while the wall of the gallbladder showed a preponderance of streptococci.

Cross-section of the apex of the gallbladder showed fibrosis, marked dilatation of blood-vessels, hemorrhage, and marked leukocytic infiltra-tion, especially in the submucosa, and numerous bacilli and diplococci both in the mucous membrane and in the hemorrhagic peritoneal coat.

One dog injected intravenously with a mixture of the streptococcus and the colon bacillus as isolated from the stone developed a marked cholecystitis. Three dogs and one rabbit injected with the streptococcus from the stone all showed cholecystitis. One dog and one rabbit in which a small branch of the portal vein had been injected, disclosed no lesions in the gallbladder. One dog in which the gallbladder had been injected directly developed only a localized cholecystitis and peritonitis around the place of puncture. The streptococci appeared to have been washed out by the bile without having produced lesions of the mucous membranes of the gallbladder or of the bile-ducts.

Dog 102.—Injected intravenously, August 24, with the growth from 150 c.c. of an ascites-dextrose broth culture of a mixture of streptococci and colon bacilli from the center of the gall-stone.

August 26: Seemed well. Chloroformed. Gallbladder wall hemor-rhagic in areas and extremely edematous; from 0.4 to 0.8 mm. in thick-ness. Pressure caused marked oozing of a blood- and bile-tinged fluid from the cut surface. Mucous membrane covered with an adherent mucus and necrotic material, but not ulcerated. No hemorrhages in the

liver; marked hemorrhage in the first two centimeters of the common duct, and many small hemorrhages in the head of the pancreas. Lymph-glands along the ducts enlarged and hemorrhagic on the cut surface. No other focal lesions except hyperemia of the mucous membrane of the small intestine and slight turbidity of the joint fluid.

August 27: Cultures from the joint fluid negative. The blood and the bile in blood agar yielded only colon bacilli; in broth, both colon bacilli and streptococci. The gallbladder wall and lymph-gland gave colon bacilli and streptococci.

Dog 108.—Injected intravenously, August 26, with the growth from 90 c.c. of an ascites-dextrose-tissue broth culture of a pure growth of the streptococcus from the gall-stone.

August 29: Seemed ill. Chloroformed. The gallbladder contained many circumscribed hemorrhages surrounded by moderate edema. These were most marked over the fundus and along the attachment of the gallbladder to the liver. Mucous membrane hyperemic with a few small hemorrhages. Liver, ducts, and pancreas appeared normal. Joint fluid distinctly turbid.

August 31: Cultures from the bile and the liver gave a pure growth of the streptococcus, while the blood and the joint fluid remained sterile.

Case 140.—A woman, thirty-four years of age, with acute and chronic cholecystitis. The symptoms suggesting gall-stones and chole-cystitis had been present for five years, but the last attack, during which she had intense pain in the epigastrium, accompanied by a moderate temperature and the development of a leukocytosis, had continued for twenty days. The patient was operated on August 22, 1914, as the symptoms were subsiding. There was an adherent, edematous, hemor-rhagic, and much thickened gallbladder, containing six stones and much pus. One of the stones was impacted in the cystic duct. The appendix was thin and fibrous, its lumen obliterated. The gallbladder was re-moved and cultures made from a portion of the wall, 1 cm. square, from near the fundus, from the center of one stone, and from the fluid contents.

August 23: The shake cultures in ascites-dextrose agar from the center of one of the stones showed approximately 7200 colonies of the typical streptococcus; those from the emulsion of the wall of the gall-bladder yielded 40 colonies of the same streptococcus (Fig. 139); the pus was sterile.

August 24: Blood-agar plate cultures from single colonies in the shake culture showed a pure growth of small, grayish, non-adherent, non-hemolyzing colonies of streptococci.

Sections across the apex of the gallbladder disclosed marked fibrosis, thickening of blood-vessels, atrophy of mucous membrane, hemorrhagic infiltration, chiefly in the submucosa and the peritoneal coat, numerous eosinophiles in connective tissue, and a moderate number of Gram-

staining diplococci in hemorrhagic areas in the submucosa and the sub-peritoneum (Figs. 134 and 135).

The streptococcus from the stone and that from the wall of the gall-bladder were each injected, in the second generation, into one dog and one rabbit. Both dogs (100 and 101) developed marked cholecystitis, but the rabbits appeared well forty-eight hours after injection. The dog injected with the culture from the gallbladder had two small hemorrhages in the tricuspid valve, hemorrhages in the diver-ticulum of Vater, and one hemorrhage in the gall-bladder. The other had two small hemorrhages in the tricuspid valve and a few in the subcutaneous tissue, but no lesions of the gallbladder or bile-ducts. The strain from the wall of the gallblad-der after cultivation on

Fig. 134.—Section of a gallbladder, Case 140, showing marked fibrosis, marked subperitoneal hemorrhage, and leukocytic infiltra-tion. Hematoxylin-eosin (× 105).

blood agar for ten days, and then in ascites-dextrose broth, was injected into three dogs. All three seemed well soon after injection, and were chloroformed, two, four, and six days later, respectively. Dog 128 had a few fading hemorrhages in the fundus of the gallbladder. The others had no lesions. A 30 c.c. portion of the suspension containing pieces of tissue in the second culture, which was injected into one rabbit and one dog and which produced marked lesions of the gallbladder, was placed in the ice-chest August 24, 1914, and the bacteria allowed to remain in latent life undisturbed until March 15, 1915. Blood-agar plate cultures then contained many small non-hemolyzing grayish colonies exactly as when isolated.

March 16: Two dogs were injected, one with 3 c.c. and the other with 12 c.c. of this old sus-pension. Both died in twenty-four hours, show-ing marked hemorrhage and edema of the gall-

Fig. 135.—Diplococcus in hemorrhagic area shown in Fig. 134. Gram-Weigert (× 1000).

bladder and hemorrhages of the stomach, duodenum, and intes-tinal tract. The one receiving 12 c.c. had, in addition, hemorrhage and edema of the cystic and common ducts. In the blood of both were pure cultures of a slightly green-producing streptococcus; in

the bile and the edematous fluid were countless numbers of the injected streptococcus.

The streptococci in the first subculture in ascites-dextrose broth from the old suspension were injected March 18 into two dogs. Both developed lesions in the gallbladder, one a few hemorrhages in the stomach, and the other a few hemorrhages in the pancreas. Both dogs were well when chloroformed forty-eight hours after injection; the blood was sterile.

A culture in ascites-dextrose broth made directly from the edematous gallbladder of the dog which had been injected with 12 c.c. of the old suspension, was injected into one dog and one rabbit. Both developed marked lesions of the gallbladder. The strain from the dog's gallbladder, injected into one rabbit, gave rise to no lesions of the gallbladder, but caused multiple arthritis. The strain from the rabbit's gallbladder was injected into three dogs and two rabbits in doses ranging from 2 to 75 c.c. All the dogs and one of the rabbits developed cholecystitis. Two weeks after the injection the gallbladders of one rabbit and one dog showed healing cholecystitis with distinct fibrous thickening.

The fact that such small amounts of the old suspension were so toxic and showed the same striking affinity for the gallbladder as did this strain in fresh cultures afforded excellent opportunity to test whether or not there was present in the streptococcus cultures a filterable virus, and whether or not streptococci from cholecystitis

Fig. 136.—Cholecystitis in Rabbit 188 five days after intravenous injection of the streptococcus shown in Fig. 139, after it had been kept in the ice-chest for seven months and then passed through Dog 275 (× 1½).

having marked affinity for the gallbladder produce soluble products with the power to cause lesions electively in the gallbladder. A dog injected with 2 c.c. of the old filtered suspension—which had been proved sterile by cultures in ascites-dextrose broth and on blood-agar—had a number of small hemorrhages in the peritoneal coat near the apex of the gallbladder and a few in the mucous membrane near the fundus. Cultures from one hemorrhagic area yielded a pure growth of the streptococcus, which evidently passed through the filter in small numbers, because subsequent cultures from the centrifugalized sediment of a portion showed the streptococcus.

Filtrates of the first subculture of this aged suspension and of the twenty-four-hour broth culture, after one and two animal passages, were injected into five dogs and one rabbit; only one dog developed lesions of the gallbladder. Cultures from the hemorrhagic gallbladder and from the blood in this dog remained sterile, and 45 c.c. of this sterile culture from the hemorrhagic area in the gallbladder failed to produce lesions in the gallbladder on subsequent injection. A filterable virus, therefore, appears absent, but there seem to be soluble products in these young cultures which, in distinctly smaller amounts than are required of similar filtrates from other streptococci, tend to produce lesions in the gallbladder when injected intravenously.

The piece of tissue added originally to the dextrose broth and con-

Fig. 137.—Gallbladder of Dog 450 seventy-two hours after intravenous injection of a subculture of the streptococcus shown in Fig. 139, after it had been kept in the ice-chest for twenty months (natural size).

Fig. 138.—Two diplococci in the hemorrhagic area in the subperitoneum of the dog's gallbladder shown in Fig. 137. One diplococcus in partial focus. Gram-Weigert ($\times$ 1200).

tained in the suspension which was kept in the ice-chest nine months, was preserved in the bottom of a test-tube in the ice-chest until March, 1916, twenty months after the cultures had been made. Subcultures from this were now made on blood agar and into ascites-dextrose broth. One ringtail monkey, one dog, and one rabbit were injected with the growth in ascites-dextrose broth. All seemed well seventy-two hours after injection, when they were chloroformed. All had developed lesions of the gallbladder (Fig. 137), but practically no lesions in other organs. The streptococcus was found in the hemorrhagic area in moderate numbers (Fig. 138).

Dog 100.—Injected intravenously, August 24, with the growth from 45 c.c. of an ascites-dextrose-tissue broth culture.

August 26: Seemed well. Chloroformed. Gallbladder filled with turbid bile; the wall edematous and hemorrhagic (Fig. 140). Mucosa normal. No hemorrhages along the ducts or in the liver, and no other noteworthy lesions.

August 27: Cultures from blood, kidney, liver, bile, and joint-fluid sterile.

DOG 101.—Injected intravenously, August 24, with the growth from 90 c.c. of an ascites-dextrose-tissue broth culture of the streptococcus isolated from the gallbladder wall.

August 26: Seemed well. Chloroformed. Acute hemorrhagic chole-

Fig. 139.—A smear of a twenty-four-hour culture in ascites-dextrose broth of a streptococcus isolated from the gallbladder in Case 140. The morphology, size, and grouping are typical of the various strains isolated in cholecystitis. Gram strain (× 1200).

Fig. 140.—Hemorrhage and infiltration in the gallbladder of Dog 100, forty-eight hours after intravenous injection of the streptococcus shown in Fig. 139 (three-fourths natural size).

cystitis. The wall of the gallbladder was covered in areas with a fibrinous exudate and contained the large subperitoneal hemorrhages, particularly over the fundus, associated with moderate edema. No noteworthy changes in the mucous membrane. Ducts free from hemorrhage. Lymph-glands along the cystic and common ducts enlarged and hemorrhagic on the cut surface. Joint fluid slightly turbid.

August 27: Cultures from blood, joint fluid, bile, and liver were sterile, while those from the infiltrated wall of the gallbladder contained the streptococcus. Sections through a hemorrhagic area near the fundus

of the gallbladder showed a layer of fibrinous exudate rich in leukocytes covering the peritoneal coat, leukocytic infiltration of the peritoneal and subperitoneal layer, especially in localized areas surrounding blood-vessels and dilated lymph-spaces (Fig. 141), and an aggregation of leuko-cytes in a rather large blood-vessel in the subperitoneum. The mucous membrane and the aggregation of lymphoid cells in the submucosa were free from lesions and revealed no leukocytic infiltration.

A moderate number of diplococci and a few short chains were in the exudate covering the peritoneum and in the areas showing leukocytic infiltration (Fig. 142).

Fig. 141.—Section of the gallbladder of Dog 101, forty-eight hours after intravenous injection of the streptococcus shown in Fig. 139. Marked leukocytic infiltration in the submucosa, between the muscle bundles of the muscular coat, and in the peritoneum. The latter is covered with a thick layer of exudate, rich in red blood-corpuscles and leukocytes. Hematoxylin and eosin (× 60).

Fig. 142.—Diplococci in the peritoneal exudate shown in Fig. 141. Gram Weigert (× 1200).

DOG 128.—Injected intravenously, September 3, with the growth from 75 c.c. of an ascites-dextrose broth culture of the streptococcus isolated from the wall of the gallbladder ten days previously.

September 5: Seemed well. Chloroformed. A few small hemorrhages in the mucous membrane of the stomach and a number of small fading subperitoneal hemorrhages over the fundus of the gallbladder. No noticeable associated edema or infiltration. Gallbladder distended with greenish bile and viscid mucus.

September 7: Cultures on blood-agar from blood and bile were sterile, while those from the blood in dextrose broth yielded a pure culture of the streptococcus.

CASE 166.—A young man, with acute cholecystitis and pancreatitis of ten days' duration, was operated on October 12, 1914. A markedly edematous, pus-containing gallbladder was found, embedded in a mass of fibrinous adhesions. The pus from the lumen and a portion of the wall of the gallbladder were removed and cultured. Smears from the former showed what appeared to be colon bacilli and streptococci.

October 13: Cultures from the wall of the gallbladder and from the pus gave three varieties of colonies, one of which appeared to be colon bacilli, another B. mucosus, and a third smaller and more opaque variety resembled staphylococci.

October 15: Subcultures on Loeffler's serum of the staphylococcus revealed a moderate amount of gray growth. The mucoid colonies were made up of strictly aërobic encapsulated Gram-negative non-motile bacilli, which did not produce gas in dextrose-agar stabs, while the colon-bacillus-like colonies showed typical non-encapsulated, motile, gas-producing bacilli.

A suspension in NaCl solution of pus failed to produce lesions in the one dog injected. A mixture of the staphylococcus and of B. mucosus injected into one dog produced numerous hemorrhages in the stomach, the small intestine, and the medulla of the kidney, and acute hemorrhagic pancreatitis with fat necrosis, while the one rabbit which was injected died with marked hemorrhages in the stomach and the intestine. The staphylococcus after one animal passage was injected into two dogs and one rabbit. Both dogs had pancreatitis and one had cholecystitis, while the rabbit had endocarditis and myocarditis.

Dog 190.—Injected intravenously, October 15, with the growth from 15 c.c. of an ascites-dextrose broth culture of the staphylococcus and the encapsulated bacillus mixed.

October 16: Found dead, body warm. Numerous small hemorrhages and erosions in the mucous membrane of the stomach, marked enteritis, and marked hemorrhages in the medulla of the kidney. Pancreas hemorrhagic and studded with numerous irregular white areas of fat necrosis.

October 17: The blood and the pancreas showed staphylococci in pure culture.

Dog 195.—Injected intravenously, October 21, with the growth from 5 c.c. of an ascites-dextrose broth culture on the staphylococcus after two animal passages.

October 23: Seemed ill.

November 6: Seemed well but had lost in weight. Chloroformed. Pancreas swollen, hard, and hyperemic. Bile thick and dark, containing mucus in which were embedded numerous black particles. On the wall of the gallbladder was an opaque band of fibrous thickening, running from the apex over the fundus.

November 11: Cultures from the bile on dextrose agar yielded a large number of Gram-staining cocci singly, in twos, and in groups. The blood was sterile.

CASE 230.—A woman, thirty-two years of age, was operated on December 30, 1914. Gallbladder edematous and distended with muco-purulent material, in which were embedded numerous small stones. Chills and fever, intense pain, and tenderness over the gallbladder had

Mucous membrane edematous, hemorrhagic, gangrenous in areas, and covered with a thick adherent mucus. Stomach, duodenum, and intestinal tract showed no noteworthy changes. Joint fluid clear.

RESULTS OF ANIMAL EXPERIMENTS

The foregoing details will serve to illustrate the results obtained in other cases. In Table 2 is given a summary of the animal experiments made with strains from cholecystitis.

Of animals injected with the strains when isolated, 79 per cent. developed lesions of the gallbladder. This is in marked contrast to an average incidence of lesions in the gallbladder of 11 per cent. as previously pointed out,[6] and to an incidence of 3 per cent. in 396 animals following injection of bacteria from sources other than cholecystitis. Later, that is, after cultivation on artificial media for a time, this affinity was found to have largely disappeared, just as it tends to disappear after successive animal passages, lesions in the gallbladder occurring in 7 per cent. and 56 per cent. of the animals respectively (Table 1). If, however, the bacteria are placed in latent life, as occurs in the single colonies in shake cultures, or in NaCl suspensions containing tissue in the ice-chest, the characteristic affinity may be retained for a long time. Thus the streptococcus from Case 140 lost nearly all its affinity for the gallbladder after cultivation on blood-agar for ten days, whereas when kept in the ice-chest in NaCl solution its affinity for the gallbladder was marked eight and twenty months later.

The incidence of pancreatitis, following injection of the strains from cholecystitis as isolated, was 5 per cent.; after cultivation, 0 per cent.; and after animal passage, 19 per cent. In some of the animals, especially those injected with strains after animal passage, there were noted simultaneously lesions of the gallbladder, bile-ducts, and pancreas (Fig. 144).

Elective affinity for the gallbladder was shown by 16 strains of streptococci from cholecystitis as isolated. Most of these were isolated from the wall of the gallbladder, 3 from the centers of gall-stones, and 1 from an adjacent lymph-gland. Only 22 per cent. of the animals, chiefly rabbits, died from the effects of the injection; the rest were killed. The colon bacilli from 3 cases of cholecystitis with stones, in which streptococci also were isolated, showed no special affinity for the gallbladder, while 2 strains from acute cholecystitis in which streptococci were absent showed marked affinity for the gallbladder. This suggests that they were secondary invaders in the former, and the cause of cholecystitis in

TABLE 1.—SUMMARY OF THE RESULTS

Case	Sex and Age	Anatomic Diagnosis	Duration of Symptoms	Results of Cultures from	
				Bile or other fluid contents of gall-bladder	Gall-stones
41	..	Cholecystitis with stones	..	..	Colon bacillus
55	..	Chronic cholecystitis with stones	..	..	Streptococcus (1 colony)
58	F 50	Chronic cholecystitis with stones and appendicitis	20 years	Streptococcus and colon bacillus	Streptococcus
59	F 56	Chronic cholecystitis and chronic appendicitis	2 or 3 years	..	..
60	F 36	Chronic catarrhal cholecystitis	10 years	Negative	..
61	F 59	Chronic cholecystitis with stones	15 years	Sterile	Streptococcus
66	M 75	Chronic cholecystitis	9 years	Streptococcus and colon bacillus	..
67	M 56	Chronic cholecystitis	10 years	..	..
68	F 50	Chronic cholecystitis with stones	16 years	..	Streptococcus and B. welchii
70	F 28	Chronic cholecystitis with stones	2 years	Negative	Streptococcus (3 colonies)
73	M 52	Chronic catarrhal cholecystitis and appendicitis	12 years	Negative	..
79	M 53	Chronic cholecystitis with stones	24 years	Staphylococcus	Streptococcus
85	M 60	Cholecystitis and pancreatitis	5 months	Streptococcus, colon bacillus, and fusiform bacillus	Streptococcus and colon bacillus
91	M 48	Gangrenous gallbladder and encysted stone	9 months	..	Streptococcus (60 colonies)
93	M 32	Pancreatitis, cholecystitis, and appendicitis obliterans	..	Negative	..
94	M 58	Cholecystitis, probably secondary to perforating duodenal ulcer	20 years	Colon bacillus	Colon bacillus and streptococcus
98	F 50	Chronic cholecystitis with stones	12 years	Streptococcus and diphtheroid bacillus	Streptococcus
99	M 24	Chronic cholecystitis	5 months	Negative	..
101	F 41	Chronic cholecystitis with stones	2½ years	Colon bacillus	Streptococcus and B. welchii
102	M 55	Chronic catarrhal cholecystitis	6 years	Colon bacillus	..
108	F 52	Chronic cholecystitis with stone	25 years	..	Streptococcus
115	M 44	Chronic cholecystitis with stones	3 years	Negative	Negative
117	F 45	Acute cholecystitis with common-duct stone	4 or 5 years	Colon bacillus	Streptococcus
120	M 55	Cholecystitis with stone and duodenal ulcer	7 years	Negative	Streptococcus, colon bacillus, and B. welchii
122	F 49	Chronic catarrhal cholecystitis with stones	17 years	Negative	Negative
124	F 39	Chronic cholecystitis with stones	22 years	Streptococcus and colon bacillus	B. welchii
128	F 68	Chronic catarrhal cholecystitis with stones	..	Negative	..
132	M 38	Chronic appendicitis and catarrhal cholecystitis	14 years	Negative	..
135	F 68	Acute and chronic cholecystitis with stones	15 years	Streptococcus and colon bacillus (many colonies, mostly colon bacillus)	Streptococcus and colon bacillus (many colonies, mostly colon bacillus)
138	F 39	Chronic cholecystitis with stones	5 years	..	Streptococcus (1 colony)

OF CULTURES IN CHOLECYSTITIS

Results of Cultures from		Remarks
Gallbladder wall	Adjacent lymph-glands	
Streptococcus (4 colonies)	..	..
Streptococcus	..	Cultures from obliterated appendix, sterile.
Streptococcus and colon bacillus	..	Cultures from appendix, streptococcus, and colon bacillus.
Negative	..	Gallbladder showed doubtful lesions.
Streptococcus (27 colonies and B. welchii	Streptococcus (5 colonies)	Cultures made from infarcted area near fundus of gallbladder.
Streptococcus and colon bacillus	..	Gallbladder had been drained for three years.
..	Streptococcus and diphtheroid bacillus	..
..	..	..
Streptococcus	..	Strawberry gallbladder.
Negative	..	Thickening of gallbladder slight. Wall of appendix showed colon bacillus and streptococcus.
Negative	..	Gallbladder contracted tightly on single stone.
Streptococcus and colon bacillus	..	Large amount of thick, tenacious, dark material in gallbladder, in which were embedded much "sand" and a number of calculi the size of wheat grains.
Streptococcus, colon bacillus, and fusiform bacillus	..	First attack of cholecystitis in which stone was probably formed, ten years before. Second attack in which stone became encysted, three and one-half months before.
Streptococcus and diphtheroid bacillus	..	Tip of appendix, portion just beyond obliterated lumen, showed colon bacillus and streptococcus.
Streptococcus (3 colonies)	..	Ulcer had probably existed for twenty years.
Streptococcus (120 colonies)	..	Symptoms of cholecystitis for twelve years. Wall of gallbladder thickened, mucous membrane destroyed. Many large and small stones.
Streptococcus or diphtheroid bacillus	..	Wall of gallbladder moderately thickened.
..	..	Wall of gallbladder only slightly thickened.
Colon bacillus	..	Gallbladder only slightly thickened.
Streptococcus and colon bacillus	..	Typhoid fever thirty years before; symptoms referable to stomach ever since, worse recently. Gallbladder wall thickened
Staphylococcus	..	Symptoms suggestive of appendicitis. No evidence of recent inflammation of gallbladder. Wall not much thickened. Stones small.
B. welchii and colon bacillus	B. welchii and colon bacillus	Patient had chills and fever at time of operation, which promptly disappeared afterward.
Streptococcus (6 colonies)	Streptococcus (1 colony)	Duodenal ulcer markedly indurated with partial obstruction to pylorus. Gallbladder and duodenum adherent.
Negative	..	Gallbladder distinctly thickened.
Streptococcus and colon bacillus	..	Mucous membrane destroyed. Wall much thickened.
..	..	Gallbladder wall slightly thickened. Stone removed and gallbladder drained.
Streptococcus (1 colony)	..	Gallbladder only slightly thickened.
Streptococcus and colon bacillus many colonies, mostly colon bacillus	Streptococcus	..
Negative	..	Only slight thickening of gallbladder. Typical strawberry gallbladder.

TABLE 1.—SUMMARY OF THE RESULTS OF

CASE	SEX AND AGE	ANATOMIC DIAGNOSIS	DURATION OF SYMP-TOMS	RESULTS OF CULTURES FROM	
				Bile or other fluid contents of gall-bladder	Gall-stones
140	F 34	Acute and chronic cholecys-titis with stones	5 or 6 years	Negative	Streptococcus (7200 colonies)
166	M ..	Acute cholecystitis and pan-creatitis	..	Colon bacillus, B. mucosus, and staphylococcus	..
168	F ..	Empyema of gallbladder with stones	..	Sterile	Streptococcus
230	F 32	Subacute cholecystitis. Em-pyema of gallbladder	..	Colon bacillus and fusiform bacillus	..
494	F 41	Chronic catarrhal cholecys-titis with stones	..	..	Streptococcus and B. welchii
497	F 43	Chronic cholecystitis with stones	..	..	..
500	F 35	Chronic catarrhal cholecys-titis with stones	..	..	Diphtheroid-like streptococcus
503	F 60	Subacute cholecystitis with stones	..	Streptococcus and colon bacillus	Negative
523	F 37	Chronic catarrhal cholecys-titis. Chronic catarrhal appendicitis	..	..	..
570	F 18	Chronic catarrhal cholecysti-tis with stones	..	Sterile	B. subtilis (2 colonies, contamination)
576	F 54	Chronic cholecystitis with stones. Appendicitis ob-literans	..	..	..
869	F 62	Subacute cholecystitis with stones	..	Sterile	Streptococcus, colon bacillus, B. welchii
971	..	Cholecystitis	..	..	Streptococcus
977	..	Cholecystitis with stones	..	..	Streptococcus
984	..	Cholecystitis with stones	..	..	Unidentified Gram-positive spore-bear-ing bacillus and ty-phoid bacillus
988	..	Cholecystitis with stones	..	..	Streptococcus
999	..	Cholecystitis with stones	..	..	Streptococcus
D	..	Cholecystitis with stones	..	..	Negative

TABLE 2.—ELECTIVE LOCALIZATION OF

SOURCE OF STREPTOCOCCI	STRAINS	ANIMALS INJECTED	PERCENTAGE OF ANIMALS SHOWING LESIONS IN.			
			Appen-dix	Stomach (Hemor-rhage)	Duode-num (Ulcer)	Gall-bladder
Cholecystitis { As isolated..........	16	53	0	29	16	79
Later..............	5	14	14	28	14	7
After animal passage..	4	16	0	31	13	56

the latter. The staphylococcus from an acute case showed marked affinity for the gallbladder. The lesions following injection of the colon bacillus and staphylococcus were not confined so strikingly to the gall-bladder as in the case of the streptococcus. Mixed cultures in ascites-dextrose broth of streptococci and colon bacilli from the gallbladder in

CULTURES IN CHOLECYSTITIS—(*Continued*)

RESULTS OF CULTURES FROM		REMARKS
Gallbladder wall	Adjacent lymph-glands	
Streptococcus (40 colonies)	..	Symptoms of cholecystitis and stone began five years before. Present attack began twenty days before. Pain severe. Gallbladder filled with pus and gallstones.
Colon bacillus and staphylococcus	..	Edematous omentum showed colon bacillus.
..	..	..
Colon bacillus, B. mucosus, and fusiform bacillus	..	..
..	..	Strawberry gallbladder.
Streptococcus and colon bacillus	..	Distal sixth of lumen of appendix obliterated.
..	..	Strawberry gallbladder. Fibromyomas of uterus. Chronic salpingitis and ovaritis.
Streptococcus (5000 colonies) and colon bacillus (few colonies)	..	..
..	Colon bacillus	Strawberry gallbladder. Obliteration of mucosa at distal end of appendix.
Diphtheroid bacillus	Sterile	Distal third of lumen of appendix obliterated.
..	Streptococcus (12 colonies)	..
Streptococcus	..	..
..	..	..
..	..	..
..	..	..
..	..	..
..	..	Cultures made one year after stones were removed.

STREPTOCOCCI FROM CHOLECYSTITIS

PERCENTAGE OF ANIMALS SHOWING LESIONS IN:									
Pancreas	Intestines	Joints	Endo-cardium	Peri-cardium	Myo-cardium	Muscles	Kidney	Lung	Skin
5	19	17	12	0	2	9	5	8	3
0	0	21	14	0	0	0	7	0	0
19	13	25	19	0	13	0	13	6	0

cholecystitis were injected directly into 11 animals; of these, 5 (46 per cent.) developed lesions of the gallbladder, while the appendix and stomach showed no noteworthy lesions. These findings are again in marked contrast to those following injections of the primary mixed cultures of streptococci and colon bacilli from appendicitis and ulcer of the stomach.

The mixed cultures from appendicitis produced lesions of the appendix in 30 (78 per cent.) of 37 rabbits, of the stomach or duodenum in 9, and of the gallbladder in 4. Those from ulcer produced lesions of the stomach or duodenum in 5 (62 per cent.) of 8 animals, lesions of the gallbladder in 1, and lesions of the appendix in none. The tendency to infect the tissues in animals corresponding to the diseased tissues from which the organisms were isolated is shown, therefore, even by mixed cultures. It should be stated, however, that in most of these the streptococcus determined the elective localization.

The elective localization of the bacteria from the tonsils was tested in the cases of three patients who had recurring attacks of cholecystitis. The cultures from two, one during an acute exacerbation, the other three days after cholecystectomy, were injected into two dogs and four rabbits. Both dogs and two of the rabbits developed striking lesions in the gallbladder, the rabbits showing lesions in the muscles in addition; the other two rabbits had ulcer of the stomach. The cultures from the tonsils of the third patient, one week after an acute attack, did not produce lesions of the gallbladder, but produced myositis in one dog and one rabbit.

Fig. 144.—Hemorrhages in the gallbladder, a, common duct, b, and head of the pancreas, c, in Dog 144 four days after intravenous injection of a streptococcus isolated from an ulcer of the stomach in man (Case 52), after one animal passage (× 1½).

In a summary of the cultures from animals with lesions in the gallbladder following injections of streptococci it was found that the streptococci were isolated from the blood at the time of necropsy in only 16 of 62 animals; from the bile in 14 of 66; from the wall of the gallbladder in 15 of 21; and from the joint fluid in 6 of 38. In 3 instances cultures from the bile or the wall of the gallbladder showed a secondary invasion of colon bacilli (Case 120, Dog 114). The number of colonies from the

wall of the gallbladder, the seat of experimental cholecystitis, ranged **from** a few to 8000.

The strains of streptococci from myositis, ulcer of the stomach, and

Fig. 145.—Localized hemorrhagic cholecystitis and hepatitis in Dog 139 three days after intravenous injection of a streptococcus from a duodenal ulcer in man (Case 112) (× 1½).

Fig. 146.—Edema of the gallbladder in Dog 142 twenty-four hours after injection of the streptococcus from the gallbladder shown in Fig. 145 (× 1½).

Fig. 147.—Cross-section of the gallbladder of Dog 63 nine days after intravenous injection of a streptococcus from an ulcer of the stomach and cholecystitis in man (Case J). Extreme edema, dilatation of the lymph-channels and connective-tissue spaces, and almost complete absence of staining of nuclei. The stomach of this dog showed two ulcers near the pyloric end, and the mucous membrane of the gallbladder was ulcerated in several areas. Hematoxylin-eosin (× 20).

after one or more animal passages, were especially prone to cause lesions in the gallbladder (Figs. 146–149, 151 and 152).

Definite formation of gall-stones, resembling in appearance those found in one of the patients in this series, was noted altogether in 6

rabbits and 3 dogs with cholecystitis (Fig. 133). In some of these animals streptococci were present in the gall-stones in pure form when absent in the surrounding fluid and salt-solution washings.

The milder lesions in experimental cholecystitis consisted of circumscribed areas of subperitoneal hemorrhage, fibrinous deposit on the peritoneum, aggregation of leukocytes in and surrounding blood-vessels (Fig. 141), while the marked changes often consisted of extreme edema from twenty-four to forty-eight hours after injection chiefly of strains from acute cholecystitis. In the former there was often marked leukocytic infiltration (Fig. 141), but in the latter this was usually absent. The nuclei of the cells in fixed tissue stained faintly, and the mucous membrane appeared necrotic (Fig. 147). Sections of these gallbladders cut transversely at the apex often showed extreme dilatation of lymph-vessels and tissue spaces which were filled with edematous fluid (Fig. 147). In size, the arteries usually appeared normal or distinctly dilated.

There was a striking difference between the location of lesions in the gallbladders of dogs following injection of streptococci and that following injection of colon bacilli. Following the former, the lesions were chiefly in the peritoneal and muscular coat, the mucous membrane being involved secondarily and only when the lesions were marked; following the latter, the mucous membrane was often necrotic or sloughed, and the peritoneal and muscular coat involved but slightly.

The demonstration of bacteria both in cholecystitis in man and in the experimental form of the disease was difficult, even where the cultures showed large numbers of colonies. This appeared to be especially true when the edematous fluid was stained with bile. In some of these colonies the bacteria appeared swollen and partially digested (Fig. 148).

THE STREPTOCOCCI FROM CHOLECYSTITIS

All strains produced acid in dextrose and maltose, and none produced acid in inulin, or in the controls of sugar-free broth; hence these are omitted in Table 3. The broth was prepared in the standard way from beef infusion, 1 per cent. of the various test substances added, the resultant media rendered 0.6 per cent. acid to phenolphthalein, sterilized fractionally, and incubated for seventy-two hours at 37° C. The number of + signs indicates roughly the degrees of acidity, with litmus or fuchsin as the indicator. The figures indicate the number of cubic centimeters N/10 sodium hydroxid required to neutralize 5 c.c. of broth culture (phenolphthalein). Unless otherwise indicated in Table 3, the strains

were isolated from the wall of the gallbladder itself. Altogether, 9 strains have been studied at intervals extending over a period of one and one-half years. These include streptococci both from the wall of the gallbladder and from gall-stones in two cases (Cases 58 and 91), and three strains before and after one animal passage. Lactose and salicin were fermented by all but one strain, mannite by all but four, saccharose by all but two, while raffinose was fermented only by two. The fermentative powers of strains from the centers of gall-stones and from the corresponding walls of the gallbladders were identical;. the fermentative powers of one strain only (Case 91) did not correspond on the different dates. Two of the strains after one animal passage showed the same fermentative powers as before (Cases 85 and 135), while one strain (Case 140) failed to ferment mannite after one animal passage.

TABLE 3.—FERMENTATIVE REACTIONS OF STREPTOCOCCI FROM CHOLE-
CYSTITIS

Date	Strain	Lactose	Saccharose	Raffinose	Mannite	Salicin
6/ 7/15	140	+++	+++	0	+++	+++
3/17/15	140	—	+++	0	+++	+++
3/28/16	140	0.7	0.4	0.2	1.9	2.5
1/21/15	140²	—	..	—	—	+
12/21/15	140²	0	0	0	0	1.5
6/ 7/15	55	+	++	0	0	0
	58	0	..	0	++	++
12/20/15	58	0.3	1.5	0	0.8	1.8
	58*	+	..	0	++	++
	85	++	..	0	++	++
12/21/15	85	1.4	0	0	1.1	2.0
	85²	++	..	0	++	++
	61	++	..	+	0	++
	91	++	..	0	++	++
1/21/15	91	+	..	—	+	+
12/20/15	91	1.6	1.3	1.0	0	1.9
	91*	+	..	0	++	++
1/21/15	91*	+	..	—	+	+
3/28/16	91*	1.1	2.7	0.1	2.2	2.6
	93	++	..	0	++	++
1/21/15	93	+	..	—	+	+
1/21/15	135*	+	..	—	+	+
	135*	+	..	0	++	++
12/20/15	135*	0.3	1.0	0	0.9	1.8
	135*	++	..	0	++	++
1/21/15	135²	+	..	—	+	+
12/20/15	135²	0.3	1.5	0	1.0	1.8
2/ 5/15	999*	+++	..	0	..	+++
2/ 3/16	999*	0.9	1.5	0.2	1.2	2.0

Figures to the right and above the numbers indicating strains represent the number of animal passages, the asterisk (*) that the strains are isolated from the centers of gall-stones The rest of the strains were isolated from the walls of gallbladders. The + sign indicates roughly the degrees of acidity. The figures indicate the number of cubic centimeters N/10 sodium hydroxid required to neutralize 5 c.c. of the broth culture (phenolphthalein).

The strains from the different cases showed a striking similarity and resembled closely the streptococci commonly found in ulcer of the stomach and appendicitis. They produced small, moist, grayish-brown or grayish-green, non-adherent, non-hemolyzing colonies on human blood-agar; they produced short chains in liquid media with clumps of cocci somewhat resembling staphylococci (Fig. 139); they were of a rather low virulence, yet somewhat more virulent than the strains from gastric ulcer and appendicitis. Five of the strains had acquired distinct hemolytic powers from prolonged artificial cultivation on human blood-agar. After animal passage they tended to produce more green on blood-agar plates. The loss of the power to infect the gallbladder electively occurred usually without demonstrable morphologic or cultural changes.

Summary and General Discussion

The results thus detailed were obtained over a period of two years, in different localities, during different seasons of the year, and in different species of animals. The number of animals injected with some of the strains was sufficiently large to prove beyond doubt the elective property of strains isolated. Streptococci and colon bacilli from acute cholecystitis gave rise to more marked lesions in the gallbladders of dogs than did those from chronic cholecystitis. In some strains the virulence could be diminished by cultivation or increased by animal passage, and the affinity for the gallbladder still retained. Usually, however, this affinity was lost. Strains grown on artificial media acquired distinctly greater affinity for the stomach and appendix; those passed through animals acquired affinity for the pancreas.[11]

In Case 120 ulcer was produced in animals with streptococci isolated from the lymph-gland draining the duodenal ulcer, and cholecystitis was produced with streptococci from the gallbladder. These results furnish experimental evidence that ulcer and cholecystitis in the same patient at times may be due to hematogenous infection by streptococci which have these respective powers of localization. A single strain, however, may have affinity for both structures, as shown in numerous experiments.

The simultaneous occurrence of lesions in the gallbladder and in the cystic and common ducts following injection of the streptococcus from the gallbladder (Case 135) where these structures were involved indicates that the lesions may be due to the wide range of affinity of the infecting microörganism. The occurrence at the same time of chole-

cystitis and pancreatitis in the animals injected with bacteria from acute cholecystitis and pancreatitis (Case 166), and with strains from chronic cholecystitis and from ulcer after animal passage (Fig. 144), suggests that the simultaneous presence of the diseases in the same patient is due commonly in the beginning to hematogenous infections and not so often to lymphogenous or local invasion as the findings at operation so often appear to indicate.[12]

The demonstration of streptococci in the involved tissues in a high percentage of cases of chronic cholecystitis, the elective affinity of these organisms for the gallbladder in animals, and the production of the disease with the strains isolated from the experimental lesions, indicate that streptococci are a cause of cholecystitis. The importance not only of draining but of removing gallbladders is apparent, especially in the absence of stones, as already emphasized by Mayo[13] and others. This is especially true in cases of chronic cholecystitis. Gallbladders removed in chronic cholecystitis during the quiescent interval have been demonstrated to be the hosts of living bacteria. Might not the periodic exacerbations be due to resumption of activity on the part of a latent infection, when the defensive mechanism of the individual is low? The fact that streptococci which produced marked cholecystitis by systemic intravenous injection failed to produce cholecystitis when injected into the radicles of the portal vein, or when injected directly into the gallbladder, is crucial evidence that cholecystitis in the absence of stones is very frequently hematogenous infection, and rarely the result of invasion from the bile.

The results of differential cultures in both spontaneous and experimental cholecystitis show that the colon bacillus is commonly a secondary invader in an infection with streptococci or in a mechanical injury produced by previously formed gall-stones. That it is the primary cause of cholecystitis in some instances is quite certain, because one of a series of strains of the colon bacillus from cholecystitis was present in pure culture and showed elective affinity for the gallbladder in animals (Case 230; Fig. 143). In one case cholecystitis which had begun during convalescence in typhoid fever was proved to be due to streptococci; hence it would seem that cholecystitis occurring in typhoid fever is not always due to the typhoid bacillus.

The common presence of bacteria in the centers of gall-stones, the formation of gall-stones in association with cholecystitis following injection of streptococci, as observed in 9 instances, and the presence of the

streptococci in the newly formed stones, emphasize anew the important rôle which infection plays in the etiology of gall-stones.[14] The almost complete absence of bacteria in the 4 pure cholesterol stones is in accord with the views of Aschoff,[15] Henes,[16] and others, who emphasize the importance of a high cholesteremia as a causative factor in the formation of gall-stones. Streptococci have been isolated from the walls of gallbladders and demonstrated there in cases of chronic cholecystitis without stones. It would appear, therefore, that for the formation of gall-stones two factors are usually necessary: (1) Infection furnishing the nucleus for the precipitation of bile salts, etc., and (2) a concentrated bile of high cholesterol content.

REFERENCES

1. Blachstein, A. G.: "Intravenous Inoculation of Rabbits with the Bacillus coli communis and the Bacillus typhi abdominalis," Bull. Johns Hopkins Hosp., 1891, ii, 96–103.
2. Welch, W. H.: "Additional Note Concerning the Intravenous Inoculation of the Bacillus typhi abdominalis," Bull. Johns Hopkins Hosp., 1891, ii, 121–122.
3. Cushing, H.: "Observations Upon the Origin of Gallbladder Infections and Upon the Experimental Formation of Gallstones," Bull. Johns Hopkins Hosp., 1899, x, 166–170.
4. Koch, J.: "Typhusbazillen und Gallenblase," Ztschr. f. Hyg. u. Infektionskrankh., 1908–9, lxii, 1–32.
5. Gay, F. P., and Claypole, E. J.: "The 'Typhoid-carrier' State in Rabbits as a Method of Determining the Comparative Immunizing Value of Preparations of the Typhoid Bacillus," Arch. Int. Med., 1913, xii, 613–627.
6. Nichols, H. J.: "Observations on Experimental Typhoid Infection of the Gallbladder in the Rabbit," Jour. Exper. Med., 1914, xx, 573–581.
7. Rosenow, E. C.: "Transmutations within the Streptococcus-pneumococcus Group," Jour. Infect. Dis., 1914, xiv, 1–32.
8. Rosenow, E. C.: "Bacteriology of Cholecystitis and its Production by Injection of Streptococci," Jour. Amer. Med. Assoc., 1914, lxiii, 1835–1836.
9. Rosenow, E. C.: "Elective Localization of Streptococci," Jour. Amer. Med. Assoc., 1915, lxv, 1687–1691.
10. Rosenow, E. C.: "The Newer Bacteriology of Various Infections as Determined by Special Methods," Jour. Amer. Med. Assoc., 1914, lxiii, 903–907.
11. MacCarty, W. C.: "The Pathology of the Gallbladder and Some Associated Lesions," Ann. Surg., 1910, li, 651–659.
12. Rosenow, E. C.: "Pathogenesis of Spontaneous and Experimental Appendicitis, Ulcer of the Stomach and Cholecystitis," Jour. Indiana Med. Assoc., 1915, viii, 458–461.
13. Mayo, W. J.: "Cholecystitis Without Stones or Jaundice in its Relation to Chronic Pancreatitis," Amer. Jour. Med. Sci., 1914, cxlvii, 469–474.
14. Mignot, R.: "L'origine microbienne des calculs biliaires," Arch. gén. de méd., 1898, ii, 129–143, 263.
15. Aschoff, L.: "Zur Cholesterinesterämie der Schwangeren," Wien. klin. Wchnschr., 1911, xxiv, 559.
16. Henes, E.: "The Value of the Determination of the Cholesterin Content of the Blood in the Diagnosis of Cholelithiasis," Jour. Amer. Med. Assoc., 1914, lxiii, 146–147.

THE EFFECT OF REMOVAL OF THE GALL-BLADDER: AN EXPERIMENTAL STUDY*

EDWARD STARR JUDD AND FRANK C. MANN

In 1887 Oddi,[1] with the object of determining the functional importance of the gallbladder, attempted to produce a continuous flow of bile into the intestine by completely removing the gallbladder from dogs. This had previously been done by Zambeccari. The animals operated on recovered quickly, and the sections made some time later showed the hepatic, cystic, and common bile-ducts dilated to twice or three times their normal caliber. The cystic duct seemed to be transformed into a reservoir for bile, and had the appearance of a newly formed gallbladder. To explain these results it must be assumed that some powerful obstacle is opposed to the continuous outpour of bile and causes the marked dilatation observed in the bile-ducts. This led Oddi to the discovery of a special sphincter of plain muscle at the duodenal end of the common duct. He says that this sphincter is entirely independent of the muscular coat of the intestine. The idea that there was a sphincter muscle at the orifice of the common duct has prevailed since the time of Glisson, but Oddi was the first actually to describe this muscle. Oddi's material did not permit him to extend his studies to the bile-ducts of man, but Hendrickson,[2] in 1898, studied in detail the entire musculature of the extrahepatic biliary system. He found that there are many individual variations in structure, but that these deviations do not alter the general anatomic bearing of this region. He concluded that a separate sphincter muscle exists at the duodenal end of the common duct in man as well as in dogs and rabbits.

Archibald[3] deserves great credit for calling attention to the action of this sphincter and the part that it may play in the etiology of pancreatitis. If pancreatitis is caused by the entrance of bile into the pancreas through the pancreatic duct, its presence in these ducts must be

caused by obstruction offered by this sphincter at the duodenal orifice. Archibald found that the pressure in the common duct can be very greatly increased by stimulating the sphincter to contract. He suggests an operation for paralyzing the sphincter as a possible treatment for pancreatitis, and has performed this operation successfully in animals.

Fig. 153.—Photograph of the under surface of the liver of a normal dog. The biliary tract is fully dilated with air.

Our experiments show that the pressure in the common duct is greatly reduced, and, as a matter of fact, may be almost *nil* some time after the gallbladder is removed. We believe this is due to the fact that after cholecystectomy the gradual increase in pressure first causes dilatation of the ducts and eventually overcomes the sphincter entirely. The bile then flows almost continuously into the duodenum and is not

forced back into the pancreatic ducts.   If this is true, it will explain what we feel sure is a clinical fact; namely, that cholecystectomy in many instances will cure pancreatitis.

Dogs, cats, and goats were used in our investigation.   The latter were employed because of the relationship of the pancreatic duct to the

Fig. 154.—Photograph of the under surface of the liver of a normal dog, approximately the same size and weight as shown in Fig. 153.   The gallbladder of this animal had been removed two hundred and fourteen days previously.   Biliary tract also dilated with air.   Marked dilatation of common and hepatic ducts.

common bile-duct.   The former enters the latter at a rather acute angle, quite a distance from the duodenum.   In the dog and cat one of the pancreatic ducts opens into the common duct near the ampulla.   All operative procedures were undertaken with the animal under anesthesia, and the usual surgical technic was employed.   At different times after operation, except when death resulted from intercurrent disease, the

Fig. 155.—Photograph of under surface of liver of a dog one hundred and twenty-two days after cholecystectomy: *A*, Stone in the common bile-duct; *B*, small stone in the ampulla of Vater.

Fig. 156.—Photograph of same specimen as shown in Fig. 155. The common duct has been opened, exposing the stone.

Fig. 157.—Photomicrographs of cross-sections of the different parts of the common bile-duct of a cat, showing the course of the duct through the duodenal wall: A, Duct immediately preceding its entrance into the muscle layer; B, duct as it is beginning to pass through the muscularis; C, duct at a point one-third of the distance through the muscularis. The pancreatic duct is shown parallel to the common duct (× 8).

Fig. 158.—Photomicrographs showing the same duct as Fig. 157, in its passage through the muscle-wall; D, Common bile-duct and pancreatic duct parallel to each other, with the former in the center of the muscularis; E, ducts still parallel; the common bile-duct almost on the mucosal side of the muscularis; F, ducts about to unite, passing through the muscularis (× 8).

animals were killed under anesthesia and the points of interest carefully examined grossly, and in many instances, microscopically.

Fig. 159.—Photomicrograph showing the same duct as Figs 157 and 158 on its passage through the mucosa. *G*, Common duct has just passed through the muscularis; the muscle is still broken; *H*, duct has apparently entered the mucosa; the muscularis mucosæ well defined; *I*, opening of the duct into the duodenum.

After removal of the gallbladder all the extrahepatic ducts dilate. This could be demonstrated in dogs and cats and, to a less extent, in goats. The dilatation varies from a very slight degree to two or three times the normal diameter of the ducts. However, no dilatation was observed in the ducts within the liver substance, and the intramural portion of the common bileduct is dilated to a less extent than the rest of the duct. The greatest dilatation of the biliary tract occurs at the juncture of the hepatic ducts coming from the upper lobes of the liver. The cystic duct was found to be dilated in a few instances. That this condition was not noted more often we attribute to the fact that usually, when a cholecystectomy is done, the cystic duct is ligated very close to its juncture with the hepatic duct (in dogs and cats the true common duct is formed below the entrance of the cystic duct). In general, dilatation of the biliary tract occurred within sixty days after the removal of the gallbladder of any dog or cat; but the time necessary for this change to be accomplished was variable. No changes were ever observed in the liver or pancreas, and even in goats the pancreatic duct always appeared normal. The following experiment is typical:

EXPERIMENT 469.—October 19, 1915. A male dog weighing 10.2 kilos. The animal was etherized and the gallbladder removed. The diameter of the common duct at the time of operation was 6 mm. The animal was killed with ether February 8, 1916. The operative field was in good condition. The common bile-duct was dilated, having a diameter of 1 cm.; after entering the wall of the duodenum its diameter was only 6 mm. The cystic duct had been completely ligated at the time of operation. All the hepatic ducts outside of the liver were dilated. The pancreatic duct seemed to be of normal size. The pancreas and liver were normal grossly and microscopically.

It is desirable to know the exact mechanism by means of which this dilatation is produced. As the increase in the size of the duct took place throughout its entire course, it is evident that the cause of the temporary obstruction and resulting dilatation must be located at its distal end. The most probable cause for this obstruction is the sphincter Oddi. The part this sphincter plays in producing dilatation of the biliary tract after cholecystectomy we have investigated by three methods: (1) By comparing the pressure withstood by the sphincter in normal and control animals; (2) by surgically dissecting the duct free from muscle-fibers in its passage through the duodenal wall at the time the gallbladder was removed; and (3) by sectioning the mucosal opening and a portion of the sphincter through a duodenal incision. The residual pressure of the common duct, as measured by a water manometer (which is practically a measure of the pressure the sphincter Oddi will withstand), is quite variable in normal anesthetized dogs and cats. Deep etherization and long periods of anesthesia, together with the exposure and trauma of handling, seem to decrease the tone of the sphincter and likewise the residual pressure. However, it is safe to say that in the normal animal, under light anesthesia of short duration, the residual pressure is always greater than 100 mm. water and usually greater than 150 mm. These figures are much smaller than those given by Oddi and by Archibald. After removal of the gallbladder the residual pressure is always very low; in some cases it was zero, and rarely was it greater than 40 mm. water. The following experiment is representative:

EXPERIMENT 124.—March 6, 1916. A black, female cat, weighing 2.3 kilos, was etherized and its gallbladder removed. The animal remained in good health after operation. August 2, 1916, it was again etherized, and the water manometer was connected to the common bile-duct. A normal cat of approximately the same size (weight, 2.2 kilos) was also etherized, and the common bile-duct attached to the same manom-

eter through a two-way stop-cock. The sphincter of the cat operated on withstood a pressure varying between 30 and 60 mm. water, while that of the control animal withstood a pressure of 160 to 170 mm. water. The common bile-duct of the cat operated on was dilated, having a diameter of 3 mm. The diameter of the common bile-duct of the control cat' measured 1.5 mm. The liver and pancreas of each animal were normal.

In those animals in which the muscle-fibers were dissected free from the intramural portion of the duct at the time the gallbladder was removed dilatation of the duct did not occur except when there was mechanical obstruction due to adhesions. The residual pressure in the unobstructed cases was always very low. The following experiment illustrates this point:

EXPERIMENT 176.—March 24, 1916. A dog, male mastiff, weighing 27.9 kilos. The gallbladder was removed and the common duct dissected free from muscle-fibers in its intramural portion. The operation was accomplished with difficulty—in one place the bile-duct was accidentally opened, but was immediately closed with one silk suture. The animal was quite sick immediately after operation, refused food, and lost weight, but soon regained normal condition. July 18, 1916, it was etherized and the residual pressure estimated. The pressure varied between 20 mm. and 30 mm. water. There were many adhesions at the site of operation, but the duct was not obstructed. The ligature on the cystic duct had cut through into the lumen, and many small, pin-point concretions were attached to it. There appeared to be a slight dilatation of the duct where the upper hepatic ducts joined. The common duct measured 7 mm. in diameter and evidently was not dilated. The liver and pancreas were grossly normal.

Section of the mucosal opening and a portion of the sphincter through a duodenal incision after removal of the gallbladder has given variable results in regard to the effect on the duct, and positive conclusions cannot be drawn. However, in one perfect experiment the same dilatation occurred as in animals in which the gallbladder had been removed:

EXPERIMENT 249.—April 27, 1916. Cat, male Maltese, weighing 3.1 kilos, was etherized and its gallbladder removed. The duodenal mucosa was cut at the opening of the common bile-duct through a duodenal incision. The animal remained in good health except for mange. July 7, 1916, it was etherized. The residual pressure in the common bile-duct was estimated and found to vary between 40 and 50 mm. water. The common bile-duct was dilated and measured 4.5 mm.

in diameter. The hepatic ducts were also dilated. The pancreas and liver were grossly normal. The duodenal opening of the bile-duct was very patulous, measuring 4.5 mm. in diameter. Both incisions were healed.

Fig. 160.—Photomicrograph showing the bile-duct and pancreatic duct in the muscle-wall (× 24).

Section of the mucosal opening of the common bile-duct is not without danger, as the following experiment illustrates:

EXPERIMENT 104.—February 21, 1916. Dog, female spaniel, weighing 13.2 kilos, was etherized and its gallbladder removed and sphincter

of Oddi sectioned through a duodenal incision. The animal remained in good health except for slight mange. August 4, 1916, it was etherized and the common duct connected to a water manometer. The

Fig. 161.—Photomicrograph of the common duct just entering the mucosa, showing the intimate relation of muscularis mucosæ to duct (× 24).

residual pressure was 100 to 120 mm. water. There were many firm adhesions at the site of the operation, but none of them in any way obstructed the bile-duct. The duodenal incision was well healed. The pancreas and its ducts were normal. The common bile-duct was cer-

Fig. 162.—Photomicrograph of one of the bile-ducts of a dog, showing a cross-section of an ascaris in the duct (× 10).

Fig. 163.—Photomicrograph showing the biliary epithelium and the ascaris more in detai (× 20).

tainly not dilated—it measured 2.5 mm. in diameter. The duodenal opening of this duct was very patulous, its diameter being 5 mm. The incision had healed perfectly. The liver appeared grossly normal. On opening the bile-duct it was noted that the remaining portion of the cystic duct was slightly dilated and contained an ascaris. One or more ascarides were found in the hepatic ducts. In the duct going to the upper right lobe there were three. The left lobe did not contain any. In some cases the ascarides were found deep in the liver-substance.

The dilatation of the common duct which takes place after cholecystectomy does not prevent the guarding of the duodenal opening by the fold of mucous membrane; this fold continues to prevent reflux of material from the duodenum into the duct. In specimens in which the duct was greatly dilated and the residual pressure very low, it was impossible to produce a passage of fluid from the duodenum into the duct, even though the intraduodenal pressure was increased enormously.

The following would seem to be the probable explanation of these facts: Normally, the liver secretes bile constantly, although the rate varies. However, because of the action of the sphincter Oddi, bile is not passed into the intestine at the same rate as it is secreted; the excess accumulates in the gallbladder. After cholecystectomy the sphincter attempts to maintain this difference between rate of secretion and rate of discharge, with the result that bile accumulates in the biliary tract. As the sphincter is able to withstand a pressure varying from 100 to 645 mm. water, and the secretory pressure of the liver varies from 230 to 360 mm. water,[4] the intraduct pressure can be considerably increased. This increased intraduct pressure produces dilatation of all extrahepatic ducts. The intrahepatic ducts are supported by the liver-tissue so they do not dilate. This process, producing dilatation of the ducts, is maintained until the biliary tract will contain as much bile as the gallbladder, or, more often, until the sphincter itself becomes dilated and is not able to withstand its normal pressure.

SUMMARY

After removal of the gallbladder all the ducts outside the liver dilate. The sphincter at the entrance of the common bile-duct into the duodenum is the chief factor in producing this dilatation. After cholecystectomy this sphincter can withstand only a small percentage of the pressure which it normally maintains. When all the muscle-fibers are

dissected free from the intramural portion of the duct, the biliary tract does not dilate after the removal of the gallbladder.

REFERENCES

1. Oddi, R.: Di una speciale disposizione di sfintere allo sbocco dell coledoco, Monitore zoologico italiano, 1894, v.   Cited by Luciani, L.: Human Physiology, London, Macmillan, 1913, Vol. ii, pp. 214–217.

2. Hendrickson, W. F.: "A Study of the Musculature of the Entire Extra-hepatic Biliary System, Including That of the Duodenal Portion of the Common Bile-duct and of the Sphincter," Rep. Johns Hopkins Hosp., 1898, ix, 221–232.

3. Archibald, E.: "A New Factor in the Causation of Pancreatitis," Trans. Internat. Cong. Med., 1913, London, 1914, Sect. vii, Surg., Pt. 2, pp. 21–27.

4. Mitchell, W. T., and Stifel, R. E.: "The Pressure of Bile Secretion During Chronic Obstruction of the Common Bile-duct," Bull. Johns Hopkins Hosp., 1916, xxvii, 78–79.

GALLBLADDER DISEASES: ETIOLOGY, SYMP-
TOMS, AND TREATMENT*

CHARLES H. MAYO

- — --

The etiology of diseases becomes clear only as the bacterial or toxic causation is appreciated. For ages we have known of specific general and local diseases by name, and the symptoms were well understood, as was. the gross pathology. However, that they were caused by specific bacteria each for itself has been known for a few decades only. We now know that the symptoms are the expressed reactions of the protein cells of the body against disease by infection or toxin in developing immunity. The finding of tubercle bacilli, typhoid bacilli, pneumococci, and similar disease-causing germs has been epoch making in the advance of medicine. It was known of several diseases before the germ was discovered that immunity developed in the person after recovery, as in measles, scarlet fever, and smallpox; and it was also known that other diseases left him less resistant or anaphylactic, as in the diseases of the lung, rheumatism, tonsillitis, etc. The effect of disease on the body and its increased or diminished resistance or method of recovery led to a consideration of these factors in the blood and tissues as they developed in a living laboratory. Serums and vaccines were made to stimulate body resistance. Drugs are already reduced to few in number, compared with the past, and these have been chosen for their effect upon the circulation, the glands of nutrition, elimination, and internal secretion, and upon the nervous system. To conform to the demands of the medical profession, drug houses are already supplied with antitoxins, serums, and vaccines. Undoubtedly the greatest advance in modern medicine is the knowledge that practically all diseases are the result of protein changes, usually from infection, and that there is some degree of bacteriemia in all infections. Formerly we considered a bacteriemia to be present only in the most grave conditions of pyemia

or septicemia. A better appreciation of the effect of bacteria in producing disease would exist if we would think of them as not all being pus producers. Some of the worst offenders are non-pyogenic. The very existence of life means a constant fight against its destructive agents until we finally succumb to them.

That the diseases of the gallbladder are of infectious origin is generally conceded, but how they occur and produce their local and general effects is as yet not generally understood.

The great advance in medicine has been the proof, by the specific reproduction of disease, that all of the local pathologic processes in the body, possibly not even excluding malignancy, are caused by infection, just as are the general specific diseases. Thus the bacteria cultivated from the deep tissues of gastric or duodenal ulcer and injected into the veins of animals will have a selective affinity for similar tissue cells and reproduce ulcer in three-fourths of the animals so treated, although the bacteria have an equal chance for location in all of the tissues of the body. This is true of appendicitis. It is also true of the actively diseased gallbladder. Cultures from such tissues when put into the blood reproduced by selection disease of the gallbladder, even to occasional stone formation, in 68 per cent. of 41 animals (Rosenow). In experimental work the ducts are resistant to the infection while the gallbladder is vulnerable. Transmutation of bacterial types from one to another of similar form through variations in culture and environment has been noted by several observers. The world is indebted to Rosenow for the proof of this and for the discovery that the specific selective affinity of bacteria for similar tissues is so widely varied. This includes nerve lesions and those of the spinal cord, production of localized herpes, iritis, retinal hemorrhages, neuritis, rheumatism, nephritis, and myositis all coming into the same class of specific diseases which can be reproduced in animals from bacteria cultured from the tissues. Strains developed from the gallbladder carried through artificial media develop gastric ulcer in an increasing proportion. Culture from animal to animal increases infective pancreatitis in side-chains.

While it was conceded that these diseases of the gallbladder were due to infection and also that stones resulted in the same manner, we now have proof that stones long since removed from the gallbladder may retain living bacteria for years. Where formerly the gall-stones were considered the entity, infection now takes first place; the stones are of secondary production and often do not occur

in the more severe types of infection, as in strawberry gallbladder. The nearly pure cholesterol stone probably occurs with less infection than any other form and is usually free from bacteria. Payr has shown that the bile of pregnant women contains much more cholesterol than that of non-pregnant women or of men. Chronic infection, or infection occurring during this period with stasis and the excess of cholesterol, has something to do with the fact that four out of five cases of gall-stone occur in women, and of these about the same percentage have borne children; in many of them the first attack occurred during pregnancy.

Infection being the necessary factor, its origin has led to several theories: First, that the bacterial life of the intestine ascended the common duct and entered the gallbladder; second, that the portal circulation took living bacteria to and through the liver, entering the bile from the liver side. It has also suggested that bacterial invasion could occur by way of the lymphatic channels. The first two theories imply that the bacteria, once gaining entrance to the bile in the gallbladder, enter into and destroy its mucous lining. While this is not an utterly inconceivable theory, it must be remembered that the mucous lining is constructed for surface protection and should be as resistant as the skin. Rosenow, however, has shown that the structure is vulnerable to an attack in the rear, through the vascular system. Bacterial infarcts of the capillaries at the base of the mucous membrane cause local and general inflammation of the structure, local areas of necrosis with bile-stained tissue occurring in the so-called strawberry gallbladder. Typhoid fever is a fairly common source of diseased gallbladders, and in the so-called typhoid carriers this organ is undoubtedly the common offender. In typhoid fever the blood is teeming with bacilli and the attack is through the vascular system.

Possibly 20 cases of congenital absence of the gallbladder in man have been reported. There are several animals, the deer, horse, rhinoceros, and a few others, that do not have gallbladders, but have proportionately larger ducts. The gallbladder in the human subject, when at rest, holds about an ounce of bile. It enters the common duct of the liver at an acute angle. The duct above this point is known as the *hepatic* duct, and below it as the *common* duct. In about 62 per cent. of people the common duct passes through the head of the pancreas, and into the wall of the duodenum between the muscularis and mucosa, joining the pancreatic duct just before opening into the intestine behind a considerable fold of overhanging mucous membrane.

˒ Possibly an ounce of bile is delivered an hour and 50 ounces of secre-
tion, including that of the pancreas, may pass the duct in a day. The
mechanics are much like those of a perfume atomizer with a bulb.
Under normal conditions of flow it should be able to create a negative
pressure in the pancreatic duct as a stimulus of secretion. In 38 per
cent. of people the common duct does not go through the head of the
pancreas, but passes through the wall of the intestine in the same man-
ner. Coffey's experiments show that in cadavers the duodenum can be
burst by distention with gas or fluids before regurgitation can occur into
the common duct. Moreover, Archibald has demonstrated a small
automatic valve at the opening of the duct into the intestine. This
general mechanism explains how a hardening of the head of the pan-
creas in a patient whose common duct passes through it would result in
jaundice, while such an occurrence in one of the other type might not.
The mechanism of duct union, common and pancreatic, indicates the
manner in which the pancreas can become involved secondarily in in-
fections, especially obstruction of the ampulla by a stone. The lym-
phatic drainage from the head of the pancreas passes through the lymph-
glands of the common and hepatic ducts. A cholecystitis causing great
enlargement of these glands can produce duct pressure and jaundice or
a lymphedema or a lymph-borne infection of the head of the pancreas
may occur, just as at times lymphedema is seen in the arm following
amputation of the breast and removal of the axillary glands. The
gland group in both instances drains three regions.

The gallbladder in health is capable of expanding to contain several
times its ordinary capacity without the consciousness of the person,
unless there is obstruction causing cramping or spasm of its muscular
structure or infection of its wall, in which case it can neither expand nor
contract without the knowledge of its possessor. Herein lies the cause
of certain symptoms noted in disease. While the gallbladder itself is
looked upon by some as an unnecessary organ, it has something of a
function, although not an essential one. Man, being an omnivorous
feeder, often eats food that is slow of digestion or active in producing
gas. A fair amount of distention of the duodenum by fluids in stasis or
by gas would necessarily partially obstruct the common duct by flatten-
ing that structure in the wall of the bowel, thus calling upon a reserve
capacity which would distend the gallbladder until its muscular
structure empties it against the duodenal pressure by rhythmic con-
traction, just as the ureter normally empties urine into either an

empty or a full bladder—in health a wholly automatic or unconscious action. The common duct is stiffer walled but almost similar in structure to the gallbladder, and whenever there is congenital absence of the gallbladder or it is diseased or removed, the common duct is found enlarged. The cystic duct enters the common duct at an acute angle, and in compression of the gallbladder the pressure is exerted on the common and not on the hepatic duct. Infection is so severe at times as to cause local peritonitis, which results in adhesions of stomach, bowels, and omentum about the gallbladder or to the adjacent liver, all of which mean bacterial invasion. In the presence of stagnation, bile salts, and an excess of cholesterol the infection may be sufficient to produce stone. The original infection may not cause peritonitis and may clear up, leaving stones in an otherwise healthy gallbladder. These might be retained for many years unrecognized, and the only symptom would be mechanical obstruction. Should obstruction by stone in the cystic duct occur and persist, a cystic gallbladder, or possibly empyema or cancer, is developed as a terminal result. Cholecystitis may persist for many years with or without stones. In these cases, infection being the factor, reflexes, usually gastric, are more strongly marked, attacks of colic may occur, not so severe as in stone, there is more tenderness which lasts for several days instead of disappearing as in stone colic without cholecystitis, and local tenderness is greater. Qualitative food dyspepsia is marked—greases, raw apples, and foods of slow digestion cause much gas and gastric stasis as reflex symptoms. Severe infection (strawberry gallbladder) is often mistaken for duodenal ulcer. Although not free from some symptoms at all times, these patients have recurrence of spells or attacks of from one to three weeks' duration, with prolonged intervals of great improvement, much like those seen in ulcer. The gastric symptoms, however, when severe, are not of the type that occurs regularly and on an empty stomach, but before meals, two or three hours after meals, or in the night; the gastric delay may cause nausea or vomiting (the latter often being induced for relief), but may be quieted by soda, as in ulcer, which still further complicates the diagnosis. The recurrence of attacks undoubtedly means that the original focus, probably connected with the mouth or possibly the appendix, is still active, and the recurrence of symptoms is similar to the recurrence of rheumatism under like circumstances. Moreover, both lesions, ulcer (gastric and duodenal) and cholecystitis, may occur in the same individual and be originally caused by the same bacteria. As Rosenow has shown,

while the great proportion of reproduced disease occurs in similar tissues,
various side lines of involvement of other tissues occur, although in much
lower percentages.   Chronic infections retained in the gallbladder are
often the source of headaches and myocardial degeneration with associ-
ated nephritis.   The x-ray becomes a valuable aid in differential diagno-
sis, but too much dependence must not be placed upon the interpreta-
tion of its shadow report against history and symptoms for the diagnosis
of either gastric lesions or gall-stones; we must remember that infection
is the entity and gallstones are secondary to it; that although gall-stones
can often be shown in a radiograph, surely a great help, the latter cannot
show the severe infections, the papillary cholecystitis, soft stone, or in-
spissated bile.   Largely to depend upon it as now developed would be
to step back twelve years in the advance of gallbladder and gall-duct
surgery and its diagnosis.   The improvement in the x-ray diagnosis of ab-
dominal lesions has been so rapid that some obscure questions may soon
be cleared by it.

Pain at the left costal arch and in the epigastric region, which would
be quite positive of gallbladder disease if it were referred to the right, is
occasionally elicited, and such symptoms are usually a referred gall-
bladder pain, possibly a gastric or duodenal ulcer to be differentiated,
but still to be considered a surgical lesion.

TREATMENT

In treatment, remedies to relieve the intestines of stasis, a selection
of food which is easy to digest and which gives no distress according to
the statement of the patient, affords relief in the milder cases; hot
water before meals is of benefit in cholecystitis as it starts the emptying
of the gallbladder and the flow of bile before food enters the stomach
and gas formation begins, leaving the gallbladder with a temporary
reserve capacity within the limits of unconscious distention following
the meal.   Stone temporarily obstructing the cystic duct is relieved by
relaxation obtained by opiates or vomiting.

There are but few lymphatics on the gallbladder at the fundus;
some occur at the neck and more along the main ducts.   Blocking of
the cystic duct with infection of the gallbladder gives but little increase
in temperature.   Infection involving the hepatic and common ducts,
rich in lymph absorbents, is accompanied by chills and fever, the tem-
perature often reaching 104° or 105° F.   Should obstruction of the
common duct persist, it is accompanied by jaundice.   Where persistent

infection is the common factor, constipation is the rule. With associated pancreatitis, varying attacks of diarrhea are often noted, and it has frequently been seen that through some perversion of secretion of the pancreas or stimulus to the secretion of the duodenum the gastric acids disappear, with attendant disturbances of digestion.

A knowledge of the structures and function as well as the mechanics of delivery is essential to the proper surgical treatment of these diseases. That they are not well understood is evidenced by the fact that in four months, July to October, 1915, inclusive, of 370 patients coming to our Clinic for the relief of gallbladder and gall-duct disease, 48 (13 per cent.) had been previously operated on for the same condition, some of them twice. The majority of these patients were women, and a number had had the right ovary removed, a larger number the appendix, and a few had had fixation of the right kidney.

With reference to the question of gallbladder drainage—cholecystostomy or cholecystectomy—the surgeon is guided by the question of infection or the apparent usefulness of the structure. Can it perform its function, which is not a necessary one? Patients with stones originating from an infection which has subsided can be relieved by removal of the stones and drainage in a high percentage of cases. In more severe infection, with many adhesions and still further attachment of the gallbladder to the abdominal wall incident to drainage, the removal of stones relieves the patient of the acute colic of obstruction, but a greater number of, or fewer, gastric symptoms, which he terms dyspepsia, still persist. Such gallbladders should be removed, and also in all cases in which infection is the factor. How can we tell that a gallbladder is diseased? As a rule, infection thickens and whitens the gallbladder. It is often noted, however, that a blue gallbladder not only may have stones, but without stones may have serious changes in its mucosa due to infection. The lymphatic glands along the cystic, hepatic, and common ducts are always swollen in infections of the gallbladder. They are palpated with a finger through the foramen of Winslow and a thumb over the duct, and should be examined as frequently as opportunity offers in order that the surgeon may determine the size of the normal gland. A seriously infected gallbladder cannot exist without evidence of the infection showing in the glands which drain it. They are swollen also in cases of papilloma of the gallbladder, a rare condition, but one that is also due to infection and is possibly a factor in the etiology of cancer. In 2940 cholecystectomy operations at our clinic, papilloma was found in 130 cases.

It is hardly fair to base our judgment as to the present state of surgery on reports including the relative value of results in cholecystectomy or cholecystostomy which were made during the imperfect and developing period of the early surgery of these diseases, say twenty to ten years ago, or including a proportionately large series of unproved medical cases so diagnosed. Autopsies, as a rule, have been made in large numbers in charitable institutions, upon people who had suffered hardships throughout their lives or they would not have been in such institutions. The finding of gall-stones at autopsy in such individuals has led some observers to speak of them as "innocent gall-stones." As stated by W. J. Mayo, it is not the gall-stone that is innocent, but the doctor, and the late patient is unable to tell his story. The whole progress of present-day surgery in all lines has developed from the ocular observation of pathologic changes in the living made possible by aseptic surgery. Most surgeons gage their own ability and know their limitations. Cholecystostomy may appeal to them as a means of cure or of safety. Again, the drainage operation may be chosen for primary safety with later cholecystectomy recommended as probably necessary in the future, a two-stage method. Cholecystectomy requires more skill in its technic and greater care to avoid injury to the bowel, the vessels, and the main bile-duct.

Since our appreciation of the fact that infection is the prime factor, we have revolutionized the surgical treatment of this condition at our Clinic.

It will be seen from the table that the mortality following cholecystectomy is less at present than that following cholecystostomy (1.2 per cent. against 3.4 per cent.) for the last three years, or including all cholecystectomies—1.5 per cent.

From a series of form letters of inquiry sent to consecutive groups of patients who had been operated on by cholecystostomy during the past several years—none more recently than one year—242 replies were received, which showed that 53 per cent. of these patients were cured, 38 per cent. improved, and 9 per cent. not improved. Of the cured patients, 129 (49 per cent.) had stones, 11 per cent. had stones and empyema, 18 per cent. stones and cholecystitis, and 22 per cent. cholecystitis.

Draining in empyema cases should result in a shriveled, functionless gallbladder. In some cases the irritation of stones must cause persistence of cholecystitis, which disappears after their removal and drainage.

'16—18

THE RELATIVE MORTALITY OF CHOLECYSTECTOMY AND CHOLECYSTOSTOMY

CHOLECYSTECTOMIES

	TOTAL OPERATIONS	CANCERS	DEATHS	PROPORTION DEATHS. PER CENT.
1907-1909........................	304	..	4	1.3
1910.............................	111	2	..	...
1911.............................	100	2	3	3.0
1912.............................	211	7	4	1.9
1913.............................	261 ⎫	2	5	1.9
1914.............................	817 ⎬ 1,767	..	5	0.6 ⎫ 1.2
1915 (first ten months)...........	689 ⎭	..	11	1.6 ⎭
Totals........................	2,493	13	32	1.3

CHOLECYSTOSTOMIES

	TOTAL OPERATIONS	CANCERS	DEATHS	PROPORTION DEATHS. PER CENT.
1907-1909........................	1,085	..	15	1.4
1910.............................	426	2	7	1.7
1911.............................	481	2	4	0.8
1912.............................	427	1	3	0.7
1913.............................	204 ⎫	3	10	4.9 ⎫
1914.............................	157 ⎬ 435	..	4	2.5 ⎬ 3.4
1915 (first ten months)...........	74 ⎭	..	1	1.4 ⎭
Totals........................	2,854	8	44	1.5

From a series of form letters of inquiry sent to patients who had been operated on by cholecystectomy during the past several years—none more recently than one year—219 replies were received, which showed that 71 per cent. of the patients were cured, 22 per cent. improved, and 7 per cent. not improved. Of the improved patients, 48 (57 per cent.) had stones and cholecystitis, and 43 per cent. had cholecystitis alone.

CONCLUSIONS

Cholecystitis is an infective disease of the gallbladder. The bacteria are in the tissues of the gallbladder.

Infection may be mild, acute, chronic, or recurring.

Gall-stones may occur in mild infections.

Cholecystostomy or cholecystectomy without stones or local evi-

dence of infection will not improve the symptoms for which the operation was performed.

Gall-stones may cause mechanical obstruction.

Cholecystostomy (with removal of stones, if present) gives high percentage of cure only if the infection has subsided or has been maintained by stones.

Cholecystectomy with or without stones in diseased gallbladders or existing cholecystitis gives a high percentage of cure.

Reflex gastric symptoms are caused by the infection.

The infection may, through local peritonitis, cause adhesions to bowels or stomach or of the liver to the abdominal wall.

Symptoms of mild gastric trouble may be nearly constant, increase with exacerbation of infection, and subside after the subsidence of the attack, much like those of ulcer.

The etiology may be a small local focus primary in the mouth or secondary in the appendix.

Typhoid bacteriemia may be the etiologic factor.

THE RELATIVE MERITS OF CHOLECYSTOSTOMY AND CHOLECYSTECTOMY*

CHARLES H. MAYO

Better diagnosis of the diseases of the gallbladder and ducts has reduced the operative mortality on these organs to a point so low that it can be further reduced only by a part of 1 per cent. The discussion as to whether cholecystectomy or cholecystostomy is the better procedure has been kept up from the earliest days of gallbladder surgery. We now find that there is use for each in its place, cholecystectomy, however, being chosen increasingly often as the operation of choice.

To aid in the selection of the method of procedure, it is well to consider the function of the gallbladder: whether it is in any way necessary, or whether untoward results follow its removal. Is the mortality of cholecystectomy higher than that of cholecystostomy, and does the relief obtained by cholecystostomy average as high as that obtained by cholecystectomy? We must also consider the dangers of injury of the common and hepatic ducts incident to the removal of the gallbladder.

First, as to the necessity of a gallbladder: The anomaly of its absence in man is a very rare condition. While several of the clean-feeding animals, the horse, deer, rhinoceros, and a few others, do not have gallbladders, the duct in these animals is larger than in those in which the organ is present. It is our experience that the ducts are increased in size after removal of the gallbladder, and the enlargement is usually present consequent to the disease at the time of the operation. That ordinary good health may be maintained for a number of years without a gallbladder is evident from the reports obtained recently regarding 10 patients on whom cholecystectomies were performed in our Clinic more than fifteen years ago. This does not take into account the large number of patients who have been operated on for shorter periods with every evidence of success. The average age of these 10 patients at the time

of operation was 49.2 years; the oldest was sixty-seven years and the youngest thirty-seven years. The average duration of illness before operation was six and one-half years. The longest history was twelve years, and the shortest, seven months. Nine of the 10 patients are living; one had good health for two years and died following an accident.

In what way is the bile changed by the gallbladder? It has been claimed that the addition of the mucus from the gallbladder renders the bile less irritating to the pancreas (Flexner), but the bile has nothing to do with the pancreas unless there is some failure in the function of its delivery. It has been stated also that the bile drawn from the hepatic duct causes a more intense inflammation when injected into the pancreas than that drawn from the gallbladder. According to the commonly accepted theory of the function of the gallbladder, the organ is a reservoir capable of enlarging to a capacity of several ounces without consciousness of the change in size on the part of its possessor, and this elastic and muscular structure, which contracts rhythmically from eight to ten times a minute, pumps the bile into the intestine intermittently, overcoming the ring sphincter muscle of Archibald at the ampulla. On its way the bile does not reënter the hepatic duct, as the latter becomes closed from the mechanical pressure caused by the acute angle at which the cystic duct joins the common duct. Why should the gallbladder have a varying capacity? From its anatomic mechanical entrance into the intestine the duct passes through the muscularis of the intestine, and then proceeds for a short distance between the mucous membrane and the outer wall; the orifice of the duct is beneath a large mucous fold. Food of a variety that tends to form gas and stasis of the intestine can produce no harmful effect on the duct, as the greater the pressure, the more the duct entrance is closed by the mucous cuff and the flattened tube in the wall of the bowel. ·In fact, the intestine will burst before permitting any reflux. In a varying degree the common duct at the ampulla is surrounded by a portion of the head of the pancreas. When this is the case pancreatitis, tumors, or malignant diseases of the pancreas may produce jaundice.

The ducts, hepatic and common, are muscle-covered tubes and are functionally able to overcome Archibald's muscle and keep the bile moving into the intestine. Gall-stones, a solid evidence of disease, are generally conceded to be the result of a previous cholecystitis of the milder type, as it is less common to find them in the severe cases of in-

fection of the gallbladder. They are composed of the bile-salts and cholesterol, and from their centers bacteria can often be cultured. Since these stones are caused by an infection, the question arises as to whether the infection is in the bile or in the gallbladder. As to the manner of its occurrence and its effect there has been much discussion. Does the infection pass through the lymphatics? Of this there is but slight evidence, although the lymphatics are involved in cholecystitis. Do the bacteria pass backward from the intestine to the common and cystic ducts? The majority of observers believe that, because of failure in the function of the liver, which receives many bacteria through the portal circulation, all the bacteria at times are not destroyed. Therefore attenuated but living microörganisms gain entrance to the gallbladder through the bile and infect the wall by direct invasion of the mucous membrane. An elastic, muscle-walled sac lined with mucous membrane, however, is not any more vulnerable than the skin or mucous membrane in general. A great light has been thrown on the etiology of diseases of the gallbladder by the work of Rosenow, who shows that the attack is not frontal, but from the unprotected rear; that the bacteria are brought through the vascular stream to the capillary circulation of the wall of the gallbladder, and that bacterial infarctions create stasis, infiltration, thickening of the mucous membrane, and necrosis. He has shown that from acute and subacute inflammation of the gallbladder cultures of bacteria can be made only occasionally from the bile, but regularly from the depths of the tissues. When injected into the blood-stream of animals, the bacteria will produce similar acute inflammations of the gallbladder in 80 per cent. of them. In stagnation, cholesterol, salts, and bacterial cultures we have the origin of gall-stones; the worst infections do not produce them. The essential feature of cholecystitis being infection, we should find the lymph-glands draining the gallbladder enlarged. This is a most important point in the diagnosis, especially in those cases in which there is a little thickening but no adhesions. There are always three, and there may be six, glands on the common, hepatic, and cystic ducts. In duodenal ulcer and disease of the head of the pancreas these glands may be found enlarged. It is very necessary for the surgeon to accustom his tactile sense to their normal size, as much depends on their evidence.

Cholesterol is an important constituent of gall-stones which are large in bulk and light in weight. It is found to be increased in amount in the blood of adults with growing cells, whether they are cancerous or em-

bryonic. Its relationship to cell growth as the cause or effect is still under discussion, but it is known that 75 per cent. of gall-stones occur in women, and that in 80 per cent. of these women the symptoms develop during the period of pregnancy. Thus have been explained certain symptoms which may be well called "qualitative food dyspepsia," which is due to certain kinds of food that develop gas, such as raw apples and the oils of salads or fried foods that are tasted long and cause (elay in digestion. The resulting stasis in the duodenum pinches the duct. A healthy gallbladder undergoes no stress or symptoms from gas because it is capable of expanding and caring for the ounce of bile delivered each hour for several hours, and by its rhythmic contraction is able to pump it through the duct into the intestine against the internal pressure. If the gallbladder is diseased, its capacity is reduced, its possessor is conscious of its expansion, and its cramping is painful. In many persons the original cholecystitis which caused the development of stones subsides. In such cases there is no associated qualitative food dyspepsia, as the capacity of the gallbladder is not reduced, and any symptoms are those of rare gall-stone colic due to obstruction of the cystic duct. These persons may carry large and irregular stones for many years without symptoms. In such cases cholecystostomy (removal of the stones and drainage) would give a very high percentage of cure, while the greater the evidence of infection, the thickening of the wall of the gallbladder, necrosis, and strawberry gallbladder, the greater the indication for cholecystectomy as a general principle.

The fact is now recognized that at least one-fourth of the diseased gallbladders do not contain gall-stones, but they cause severe colic from obstruction by balls of mucus and thick bile, and more or less constantly maintain the so-called functional disorders of the stomach. In many of them the local areas of inflammation have produced a hyperplasia which shows as papillary growths projecting from the mucous membrane. In some of these cases it is probable that the process, like other papillary growths of mucous membrane, is potentially productive of cancer, and herein lies the fallacy of depending on the roentgen ray for the diagnosis of surgically diseased gallbladders. The roentgenogram cannot show papillary growths, cholecystitis, nor the severe infections known as strawberry gallbladder, nor can it show early carcinoma. Therefore, to depend very largely on the evidence of the roentgen ray in the clinical diagnosis of gall-stones would be to step backward many years; its evidence should be merely corroborative.

In the experimental production of gastric ulcer in animals by means of cultures of bacteria obtained from gastric ulcers in man it is found that one of the marked secondary lesions produced is inflammation of the gallbladder. In the reproduction of inflammation of the gallbladder in animal experimentation carried from animal to animal there is a reduction in the percentage of cases of inflammation of the gallbladder, but an increase in the number of cases of pancreatitis—the exact condition found in surgery. Pancreatitis probably occurs rarely without an accompanying inflammation of the gallbladder, and when it does occur in persons whose common duct is obstructed by the pancreas, we have the added symptom of jaundice. A symptom of associated pancreatitis is pain in the back.

Cholecystectomy is indicated in the case of a cystic gallbladder with destroyed mucosa, empyema, and functionless strawberry gallbladder. It is indicated also in cholecystitis severe enough to give symptoms, as cholecystostomy with its temporary drainage could not eradicate the bacterial inflammation of the wall of the gallbladder. Since, as a result of the fixation of the fundus by adhesions incident to drainage, the best working part of the gallbladder becomes inactive, many patients with cholecystitis have great relief while the gallbladder is draining, but the symptoms recur after the drainage ceases. When the gallbladder gives marked evidence of associated functional derangement of the stomach, cholecystectomy should be performed whether or not stones are present. Cholecystostomy gives a high percentage of cure when the evidence of disease is slight, stones are present, and gastric symptoms are absent. In associated pancreatitis drainage of the gallbladder for a considerable period rather than cholecystectomy would be indicated, even at the expense of a second operation. Unless there are marked indications to the contrary, cholecystostomy is advisable in pregnancy and for old people whose resistance is often surprisingly lower than their clinical examination indicates.

In performing cholecystectomy the cystic duct should be early isolated, and the common duct viewed before division of the cystic duct is effected. The cystic artery must be securely ligated, as failure to accomplish this or slipping of the ligature has been the cause of numerous deaths; this artery is as large as the artery of the thyroid. The cystic duct should not be ligated or divided too close to the common duct, as in many instances a permanent biliary fistula has developed as a result

of a too low division of the cystic duct, with consequent injury to the common duct—one of the real dangers of cholecystectomy.

Adhesions of the pylorus and duodenum to the liver or gallbladder often prevent the patient from receiving the full benefit of an operation, even though the serious pathologic condition has been eliminated. If, before closing the external incision, fat does not already prevent the approximation of these structures, an apron of fat should be developed by suturing the fatty round ligament or gastrohepatic omentum to the outer edge of the gastrocolic omentum, drainage being placed between this fat and the liver.

In a paper read before the Southern Surgical Association in 1915 I reported results suggesting the relative merits of cholecystostomy and cholecystectomy. Some hundreds of letters were sent to patients who had been operated on more than a year previously by cholecystostomy or cholecystectomy. Of those on whom cholecystostomies had been performed, 53 per cent. were cured and a large majority of the remainder improved. Of those who had had cholecystectomies, 71 per cent. were cured and a large percentage improved.

During the eleven months from November 1, 1915, to October 1, 1916, we performed 43 cholecystostomies, with a mortality of 14 per cent., one-half of the deaths being those of patients with cancer; 776 cholecystectomies with a mortality of 1.77 per cent., and 102 choledochotomies with a mortality of 7.84 per cent.

CHOLECYSTITIS; CHANGES PRODUCED BY THE REMOVAL OF THE GALLBLADDER*

EDWARD STARR JUDD

— —. —

PATHOGENESIS

The etiology of cholecystitis possesses many phases of which we have no definite knowledge. We all agree that non-neoplastic surgical diseases of the biliary tract are the result of bacterial infection. There may be one exception to this statement: Archibald[1] contends—and many of us believe—that pancreatitis is often if not always due to chemical changes in the pancreas. It was formerly supposed that infection in the gallbladder was secondary to that in the biliary ducts; that infection in the ducts was more prone to subside, while that in the gallbladder would persist.

Stagnation of bile in the gallbladder is thought to be the main predisposing cause of cholecystitis. Bacteriologic study of the bile and the contents of the gallbladder of patients operated on for the removal of stones has shown sterile cultures in more than 50 per cent., according to several investigators (Deaver[2]). Attention has been called to the fact that many patients are operated on as a result of the infection rather than because of active infection, and, on this account, figures may give an erroneous impression. Several investigators have found organisms in the calculi when the bile was sterile.

There are many avenues through which bacteria may reach the biliary ducts and gallbladder. A great deal has been said about their entrance by way of the portal circulation and through the liver and hepatic duct. It seems to me there can be no question but that infection of the bile-passages may and does, at times, take place in this manner. It has also been proved that bacteria may pass from the duodenum through the ampulla into the common duct and thence through the cystic

duct into the gallbladder. However, the duodenum normally is almost free from bacteria, and infection through this channel probably does not occur as often as we formerly supposed. The frequency of the coëxistence of an ulcer of the duodenum and cholecystitis is well known. Does it not seem probable that in these cases cholecystitis is a secondary infection, caused by organisms from the ulcerated area in the duodenum which have reached the gallbladder through the common duct? According to Rosenow, it must be borne in mind that before an infection entering through the lumen of the cystic duct can reach the tissues of the gallbladder it must penetrate the lining mucous membrane, which, like similar structures in other viscera, was probably intended to resist just such an invasion. This is well illustrated in the urinary bladder, for often a markedly infected kidney will pour infected urine into the bladder for a long time before there is any evidence of infection in the bladder itself. It should be recognized, however, that infection from either the liver or the duodenum may enter the gallbladder by way of the common duct. Does it not seem probable that these organisms, especially in the presence of stagnant bile, become foci for stone-formation without necessarily producing an infection in the wall of the gallbladder?

The important and most valuable work of Rosenow[3] has not only renewed our interest in the systemic circulation as a possible route for most of those infections, but it also had a tendency to change our methods of procedure in the treatment of these cases. We know that in a large percentage of these patients the infection is really in the wall of the gallbladder and that it reaches the tissues through the blood-vessels. Rosenow has produced similar lesions in animals, and has demonstrated the selective action of the bacteria. The organisms with which his results were obtained were isolated mainly from the involved tissues or from the lymph-glands draining the infected area. Twelve strains isolated from the tissues of patients who had cholecystitis produced lesions of the gallbladder in 80 per cent. of 41 animals injected. Contrast this with the average of only 11 per cent. which was obtained with the other strains. I do not believe the importance of the systemic circulation as an avenue of infection was recognized formerly. It will be readily seen that if the infection is in the bile only, the removal of the stones and drainage will be quite sufficient, while if the disease is in the tissues of the gallbladder, drainage will afford relief only temporarily unless the infection is slight.

It is difficult to recognize all cases of cholecystitis even when the abdomen is open so the gallbladder can be seen and felt. The normal gallbladder is primarily soft and collapsible, though it is often so tense and firm that we are unable to empty it. I have noticed this condition a great many times in cases in which there was no other suggestion of inflammation. The color of the gallbladder, the consistence of the bile, the appearance and thickness of the mucous membrane, all help in making a diagnosis of cholecystitis. C. H. Mayo[4] has called attention to the enlargement of the regional lymphatics as a most important factor in determining the presence of inflammation in the gallbladder if there is no evidence of ulceration in the duodenum. Hard, nodular enlargement of the head of the pancreas has been noted in conjunction with the enlargement of the lymphatic glands. In many of these cases the clinical history may be the chief factor in determining the diagnosis, other gross lesions, such as ulcer and inflammation of the appendix, having been excluded.

Interval attacks are not nearly so pronounced in cases of chronic cholecystitis when there is considerable inflammation of the gallbladder, as in cases in which stones in the gallbladder appear to be the main factor and there is little infection in the tissues. It is essential to recognize the fact at operation that the inflammation in the gallbladder may have almost subsided, and we are obliged to depend a great deal on the clinical history. Usually it is not a good plan to base operative procedures on clinical history unless it is supplemented by pathologic findings. However, in some of these cases of cholecystitis in which the pathology is not very definite and the clinical history is clear, we are obliged to base our operation, to a certain extent, on the clinical history unless we are able to find something else that will explain the symptoms. To illustrate this point, I may say that I recall a number of patients whose histories were typical of gallbladder disease and on exploration no calculi or recognizable inflammation of the gallbladder were found. However, these patients continued to have symptoms, and after some months, or possibly several years, a second operation was performed and a definite cholecystitis, possibly with stone formation, was found. This seems to indicate that cholecystitis existed at the time of the exploratory operation, though it was not recognizable. Acute and chronic catarrhal conditions produce great thickening and edema of the walls of the gallbladder. Due to the fine white lines on the mucous membrane, chronic catarrhal or strawberry cholecystitis may frequently be recog-

nized before the gallbladder is opened, though a definite diagnosis cannot often be made until it is opened.

Malignant disease of the gallbladder occurs rarely, though in our Clinic, as pointed out by C. H. and W. J. Mayo,[5] it has always been associated with gall-stone formation. During the past year I operated on a man for recurring symptoms of gallbladder disease. He had been operated on nine years previously at another clinic, and stated that a great many stones were removed at that time. He had remained entirely well until a few months before consulting us, when there was a return of former symptoms. On exploration I found a very thick-walled gallbladder, the induration extending to the ducts and the surface of the liver. I removed the gallbladder, which proved to be malignant. No trace of stones either in the gallbladder or ducts could be found. The patient had never been jaundiced. He died about three months after returning home.

Empyema of the gallbladder, either acute or chronic, is easily recognized. The walls are thick, there is much fibrous tissue, and often complete destruction of the mucous membrane. The treatment of this condition is still a debatable question. I believe, however, that most surgeons feel there will be less mortality, all factors considered, if the gallbladder is removed. In certain cases it will seem advisable to do the operation in two stages.

Much has been said about chronic catarrhal cholecystitis in which the mucous membrane has the appearance of a ripe strawberry (Mac-Carty[6]). The principal change, grossly, consists of the erosion of the apices. These desquamations present themselves as yellow specks scattered throughout the mucosa. Often there are no stones present, though the fine white specks observed on the mucous membrane have frequently been mistaken for cholesterol stones. At our Clinic in the year 1913 we operated on 21 patients who had strawberry gallbladders with no evidence of stone formation. The appendix was removed as a secondary operation in most of these, but chronic cholecystitis was the chief pathologic lesion. In nearly every instance the symptoms were those produced by inflammation of the gallbladder. I have recently traced them by letter, and 12 of the 21 report that they are entirely well and relieved of all symptoms; 5 report that they are greatly relieved, though not entirely well; 3 report no improvement, and 1 says he is worse. The removal of the gallbladder practically cured 17 of the 21 patients. This type of cholecystitis is often found at autopsy on persons

who seem to have had few, if any, symptoms due to the inflammation; similarly, some years ago, the so-called "innocent" gall-stones were found. In reviewing the records of 577 autopsies in our Clinic on persons dying from other causes, I found 26 cases in which the pathologist had reported a chronic catarrhal condition of the gallbladder of the strawberry type, though a recognizable clinical history of gallbladder trouble had not been obtained. This means that the condition which caused death offset the symptoms of chronic cholecystitis. In all probability evidence pointing to the inflammation in the gallbladder would have been obtained in a more carefully taken general history. It certainly would have been discovered if the more important lesions which caused death had not been present. This also suggests that a certain degree of chronic cholecystitis may exist without producing much evidence of trouble.

THE FUNCTION OF THE GALLBLADDER AND THE EFFECTS OF ITS REMOVAL

The exact function of the gallbladder has never been definitely established. It is most often spoken of as the reservoir for bile. However, this theory has been questioned by many investigators, since this comparatively small diverticulum, which holds at most only a few ounces, would seem inadequate, if we consider the normal output of bile from 30 to 50 ounces in twenty-four hours. C. H. Mayo and Deaver are of the opinion that the gallbladder acts as a tension-bulb, and that during fluctuations of pressure in the ducts the gallbladder may spare the parenchyma cells of the liver from back pressure. These fluctuations of pressure probably occur as a normal consequence of digestion, or they may be due to pathologic changes—an increase or decrease in the secretory power of the liver-cells. The physiologists tell us that the secretion of bile is continuous, but that its output into the duodenum is not constant and coincides exactly with the period of digestion in which acid chyme is spurted in rhythmic jets from the stomach into the duodenum. They say that bile secreted by the liver in the interval must collect in the gallbladder, where it is condensed through the absorption of water. Flexner[7] has shown that if mucus from the gallbladder is mixed with the bile, it is very much less irritating to the pancreas.

Since so many surgeons consider cholecystectomy the operation of choice, it is interesting and important to know just what changes take place after the removal of the gallbladder. We have much evidence to

show that man may exist very comfortably and apparently indefinitely without a gallbladder. Some months ago, at my request, Mann and Sistrunk* removed the gallbladders from a number of dogs. The wounds were closed with catgut, and for that reason some of the animals

Fig. 164.—Photograph of the under surface of the liver of a normal dog. The biliary tract and a segment of duodenum are distended with air.

were lost shortly after operation. The dogs which survived have been studied at various intervals. Twelve of the first series of animals lived more than thirty days; 10 of the 12 at necropsy showed dilatation of the

* In the Laboratory of Experimental Surgery, Mayo Foundation for Medical Education and Research.

common, hepatic, or cystic duct. In some instances the cystic duct was not dilated, apparently because it had been ligated very close to the common duct. None of these animals seemed to be inconvenienced by the removal of the gallbladder. Some of them died very shortly after

Fig. 165.—Photograph of the under surface of the liver of a dog of approximately the same size and weight as in Fig. 164; the gallbladder had been removed two hundred and fourteen days previously. Marked dilatation of the common and hepatic ducts.

operation, but apparently the removal of the gallbladder had nothing to do with the cause of death. A careful examination of the animals that lived only a short time did not reveal any changes in the ducts, liver, or pancreas, while all the dogs that lived more than sixty days at autopsy showed some dilatation of the common duct. There was considerable

variation in the amount of dilatation, though the duct was usually two or three times its normal size.   Dilatation seemed to be greatest in the hepatic duct; however, it invariably stopped at the surface of the liver,

Fig. 166.—Photograph of the under surface of the liver of a dog from which the gallbladder had been removed one hundred and twenty-two days previously, showing distended gall-ducts.   A, Stone in the common bile-duct; B, small stone in the ampulla of Vater.

Fig. 167.—Photograph of the same specimen as in Fig. 166; gall-ducts opened, showing the accumulation of stones, which apparently had caused the dog no inconvenience.   No evidence of stones at the time of cholecystectomy.

and in none of the animals was there any enlargement of the ducts within the tissues of the liver, nor was there any macroscopic or microscopic change in the liver, the pancreas, or the pancreatic ducts in the several

'16—19

instances in which these organs were examined. The pancreatic ducts did not show dilatation. Unquestionably, dilatation of the ducts is at least due partly to the pressure caused by the resistance of the sphincter at the ampulla of Vater (Figs. 164–168). Oddi[8] first demonstrated the presence of this sphincter; its activity has been most carefully worked out by Archibald. Although dilatation of the ducts is probably caused chiefly by the bile's being held back by the constrictor muscles at the ampulla, eventually dilatation may overcome the action of this sphincter.
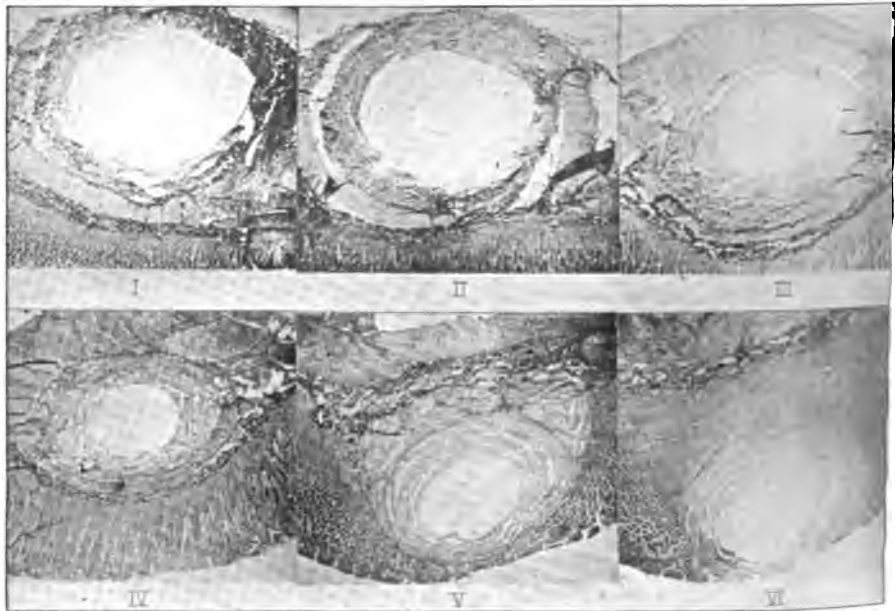
Fig. 168.—Photomicrographs of cross-sections of the different parts of the common bile-duct. No. 1 is a section through the duct just at its entrance into the duodenal wall. Nos. II, III, IV show the different intramural portions of the duct. Nos. V and VI show the passage of the duct through the mucosa. Note the change in the size of the lumen, the variation in the amount of muscle surrounding the duct, and its relation to the duodenal mucosa.

Two dogs that had had their gallbladders removed two months previously showed almost complete absence of sphincter action, and a cannula introduced into the dilated common duct carried water through the ampulla into the duodenum with no apparent resistance. An active sphincter will resist from 300 to 600 mm. of water-pressure. If we can demonstrate that the dilatation of the ducts (which follows the removal of the gallbladder) results in paralysis or laxity of the muscle at the ampulla, the cure of inflammation of the pancreas by the removal of the gallbladder may be explained.

The experiments of Opie[9] and Flexner show that the injection of bile-salts into the pancreatic ducts invariably produces pancreatitis. Why is it, then, that cholecystectomy is not always followed by a very severe irritation of the pancreas? If cholecystectomy is performed, the source of the mucus is removed. The mucus mixed with the bile apparently protected the pancreatic tissues. It would seem also that immediately after the removal of the gallbladder there should be a distinct increase of pressure in the common duct, and a considerable quantity of bile would be more freely forced back into the pancreatic ducts. Possibly this explains the rather severe reaction (especially vomiting of bile and quick pulse) which sometimes persists for a few days after cholecystectomy. We have known for a long time that removal of the gallbladder cured a large percentage of cases of pancreatitis (W. J. Mayo[10]). After a very thorough experimentation and clinical study, Archibald concludes that nearly all cases of pancreatitis are due to irritation of the pancreas as the result of bile entering the pancreatic ducts; in other words, that pancreatitis is caused by chemical rather than bacterial changes. The cure of pancreatitis which has been produced in this way would necessarily lie in the paralysis of the Oddi sphincter. This would allow the bile to flow into the duodenum unobstructed. Archibald suggests an operation which he has performed experimentally to paralyze this sphincter. From our experiments we feel sure that the dilatation of the common duct which always follows cholecystectomy will eventually result in a paralysis of the sphincter; that the bile will flow into the duodenum with little or no back pressure; and the symptoms produced by irritation to the pancreatic tissues will be entirely relieved. We are endeavoring to produce paralysis of this sphincter at the time the gallbladders are removed from animals, and in this way we try to show that the dilatation which follows is the result of sphincter action.

Dilatation of the common duct following removal of the gallbladder is frequently seen at the operating table. However, it is often complicated by stones in the common duct. I have often observed this condition in patients having hydrops of the gallbladder, and as the stone obstructs the common duct, the organ is out of commission. Often patients have not given a history of having had a stone or infection in the common duct, and at operation the duct is found markedly dilated but free from stone. A similar condition is also observed in cases of very marked cholecystitis in which the infection is so extensive that in all probability the gallbladder has ceased to functionate. For a long time

it has been known that the dilatation of the ducts called "compensatory dilatation" does result from the removal of the gallbladder. Oddi and Rost[11] have called especial attention to the condition.

If the pancreatitis which results in some of these cases is due to lymphangitis, as suggested by Deaver and Pfeiffer,[12] the removal of the gallbladder would also cure this condition, because in most instances unquestionably the primary infection is in the gallbladder, and from it extends along the lymphatics of the ducts and then into the glands throughout the pancreatic lobules. The two cases following serve to illustrate the changes to be expected after cholecystectomy:

CASE A145,438.—Mrs. J. B., fifty-six years of age, a housewife living on a farm, was examined November 10, 1915. Family history negative. There had been no previous diseases, injuries, or operations. Her chief complaint was nausea, vomiting, and pain in the abdomen. She was very weak, unable to walk, and came to the Clinic in a wheelchair. While her history was being taken she vomited several times. Her husband stated that the vomiting had begun suddenly and had persisted since August, with much bile in the vomitus and general abdominal pain. She had been able to drink some water, and thought that this had preserved her. She was markedly emaciated and prostrated. Examination of the chest and pelvis was negative. Reflexes were normal; skin dry; throat parched; tongue red; peristalsis visible, and also noticeable on palpation.

It was apparent that the woman was suffering from chronic obstruction, most likely in the intestines, though we were unable to say definitely that it was not gastric. On account of her weakened condition no further examinations were made, and it seemed best to do an immediate exploration. A right rectus incision was made November 15, 1915. The gallbladder was markedly dilated; there was considerable dilatation of the common duct, though no stones could be felt. The obstruction was caused by intussusception in the small intestine, beginning about five feet from the duodenojejuinal juncture. It was impossible to reduce the intussuscepted loop and we did a resection, removing about three feet of the small intestine. The end of the bowel was closed and an end-to-end anastomosis made. The patient did not rally from the operation and died in twenty-four hours.

Autopsy revealed an interesting condition of the gallbladder. It was markedly distended, and upon opening we found chronic cholecystitis of the strawberry type and papilloma. It was filled with a dirty, tenacious, bile-stained mucus. The gall-ducts were also markedly distended; the hepatic duct, 2 cm. in diameter, the common duct, 1 cm., and the cystic duct 1 cm. At a point 3 cm. from the gallbladder the cystic duct was obstructed by a ring of inflammatory fibrous tissue which had con-

tracted around it.   A probe could not be passed through the duct from
below upward or from above downward, neither could fluid be forced
through it.   Aside from this stricture the ducts were patent.   No stones
or inspissated bile were found in the ducts.   The liver was slightly en-
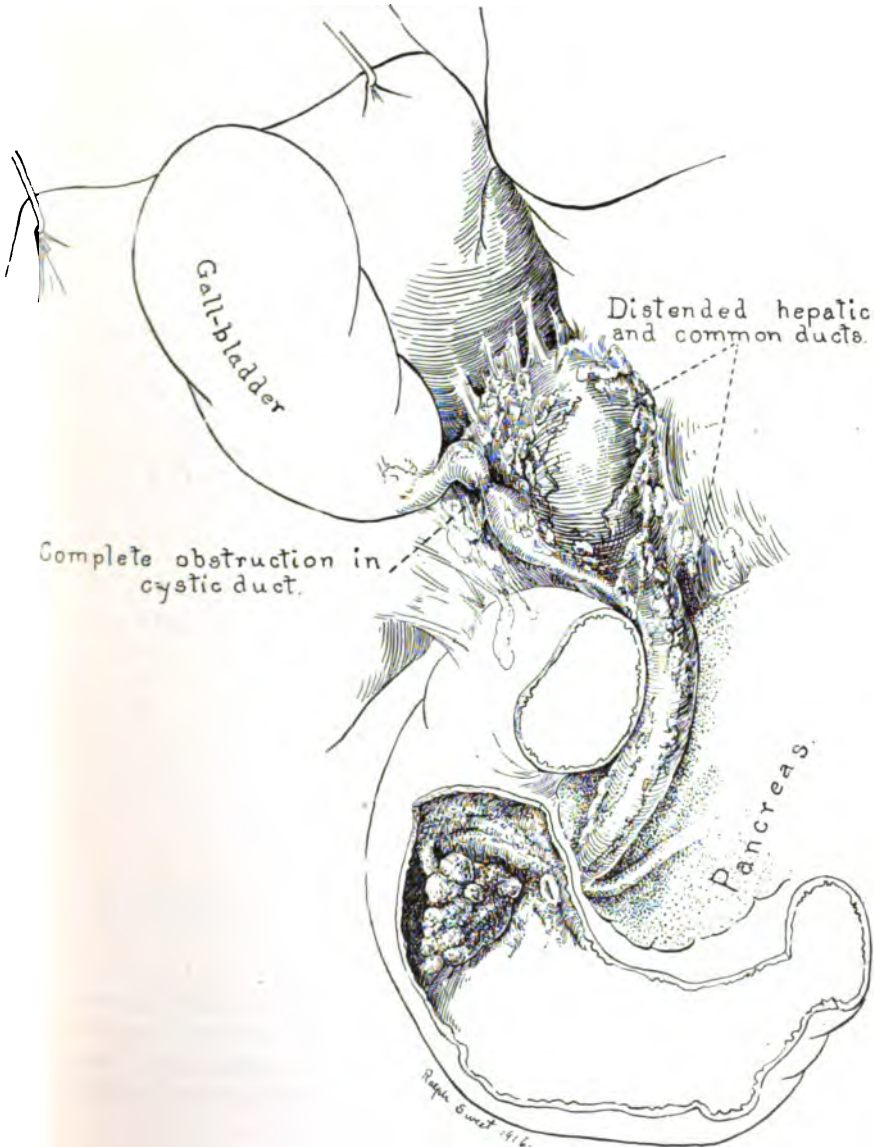
Fig. 160.—(A145,438.) Specimen removed at autopsy.   Complete closure of the cystic duct, evidently of long standing.   Common duct dilated to 12 mm. in diameter.   Stricture of the cystic duct has produced a condition similar to that following the removal of the gallbladder.

larged; the bile-ducts were filled with mucus; the pancreas, negative (Fig. 169).

We were unable to elicit a gallbladder history from either the patient or her husband, and believe that the nausea and vomiting were due to the intestinal obstruction. Of course, we could not say whether or not she had had gall-stones that had passed. Our interpretation of the features in this condition of the gallbladder was that from some cause the cystic duct had been obstructed and this had eventually destroyed the mucous membrane, leaving a stricture, with the result that the gall-bladder could no longer perform its functions, and the condition was the same as though the gallbladder had been removed. Marked dilatation of the common duct had taken place, which, as is shown in the drawings, was probably secondary to occlusion of the gallbladder from the biliary tract.

CASE A92,877.—T. H., a business man, sixty-four years of age, was examined September 29, 1913. Family history negative. This patient had had gastric symptoms off and on for twenty years, and recently he had had typical gallbladder attacks. On October 30, 1913, cholecystectomy was done. Four stones as large as pullets' eggs and three small ones were removed from the gallbladder and from a pocket in the liver into which they had perforated. The adherent omentum in an umbilical hernia was also resected, and one piece was sutured into the sac to plug the opening. Recovery was uneventful.

The patient returned December 16, 1915, giving a history of recent symptoms typical of duodenal ulcer. December 29, 1915, posterior gastro-enterostomy was performed. It was found that an ulcer of the duodenum had caused obstruction of the pylorus; the stomach was dilated, and there were adhesions about the pyloric end. The patient did well for six days, had no trouble with his stomach, took food freely, and was able to sit up in a chair. He had had bronchitis for several years, but apparently it was not troublesome. However, bronchial pneumonia developed rather suddenly and he died in seventy-two hours after the onset.

Autopsy January 7, 1916, showed a well-healed gastro-enterostomy, no leakage; the orifice admitted two fingers. Gall-ducts were patent. The common duct was dilated to 2.2 cm. in diameter; the cystic duct was not distended. Just proximal to the papilla of Vater, but apparently having no communication with it, was a small diverticulum leading from the duodenum. The diverticulum was lined with duodenal mucous membrane about 3 cm. deep and 1.5 cm. in diameter. The pancreas was rather firm and nodular to the touch and showed chronic pancreatitis (Fig. 170).

This case gave us an opportunity to observe the condition of the gall-ducts two years after cholecystostomy, which really amounted to a cholecystectomy, as the gallbladder was practically destroyed at the time of the drainage operation. The gallbladder was constricted and

held down by a mass of adhesions and evidently had not been functioning for a long time; the ducts were markedly dilated.

The two cases I have just cited are the only ones I could find in our autopsy records in which the gallbladder had been either destroyed or
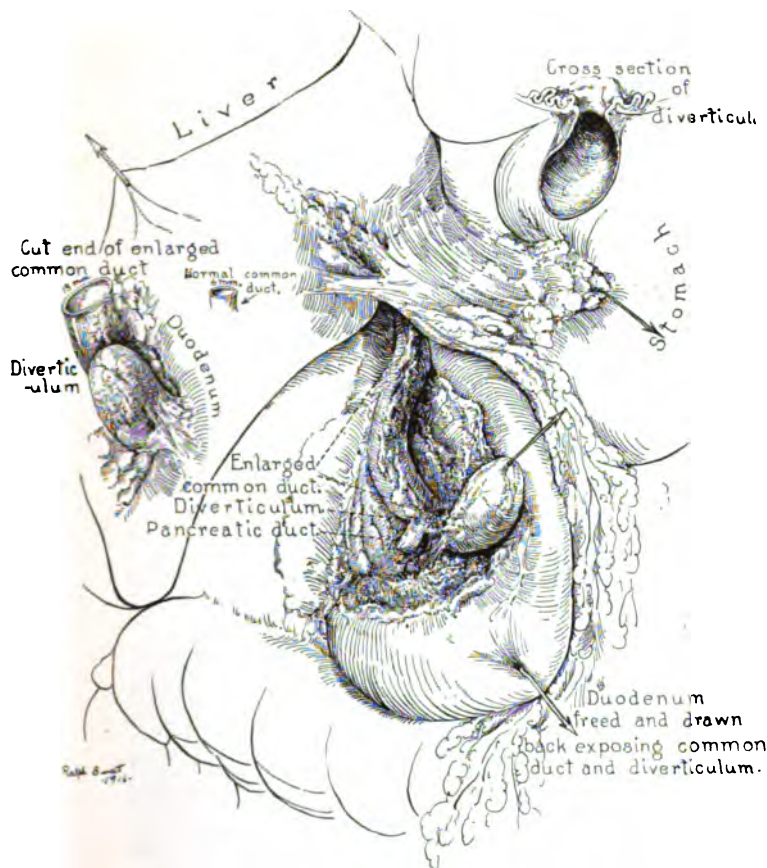
Fig. 170.—(A92,877.) Specimen removed at autopsy two years after cholecystostomy. Gallbladder entirely destroyed. Common duct markedly dilated, measuring 15 mm. Scar tissue fills space previously occupied by gallbladder.

removed some time previous to the autopsy. Although the gallbladder was not removed in either of these cases, practically that condition obtained, and the changes which took place were those that might be expected following cholecystectomy.

TECHNIC

Cholecystectomy must be considered the operation of choice if we assume that the infection is actually in the tissues of the gallbladder, and

if we know that the removal of this organ relieves pancreatitis, whether produced through the regional lymphatics or the common and pancreatic ducts. A much larger percentage of patients have recurrences following drainage, and this would seem to be an argument in favor of cholecystectomy. C. H. Mayo's[13] recent report shows that the mortality following the two operations is about the same. The gallbladder can be removed without any untoward results to the patient, and the only changes following its extirpation are those in the biliary ducts. The
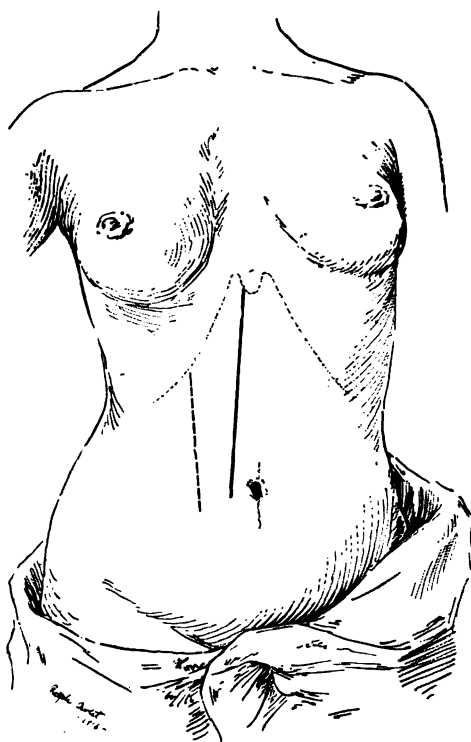
Fig. 171.—Dotted line, old incision. Black line, new incision.

drainage operation will have a place, at least until it has been shown that the infection is always systemic and into the tissues themselves. It seems to me that cholecystostomy would be the operation preferred in any case in which the infection seemed to be in the bile only and in which the tissues of the gallbladder were free.

There are a few points in the technic of gallbladder operations which I think should be emphasized. Good exposure is most essential, and this does not depend nearly so much on the size of the incision as on its

location (Fig. 171). Formerly it was customary to make the incision over the fundus of the gallbladder, but the fundus is nearly always movable, and the fixed point is at its juncture with the cystic duct. The best exposure of the gallbladder, cystic duct, and common duct is obtained by making the incision in the abdominal wall at a point just over the ducts. This will be near the midline, beginning directly beneath the

Fig. 172.—External aponeurosis of rectus muscle incised. Rectus muscle-fibers separated by blunt dissection. Black line, aponeurosis incision. Dotted line, muscle incision.

ribs, to the right of the ensiform. The best incision is the one made in a straight line through the superficial tissues and deep fascia, extending obliquely from the ensiform to a point about 2 inches to the right of the umbilicus. This is practically the Bevan incision. The next step is to reflect the fascia and separate the right rectus muscle-fibers (Fig. 172). If there is any difficulty at all in obtaining the exposure after the

peritoneum is opened, it is best to cut the suspensory ligament of the liver. This is not always necessary, but often a great help. After the ligament has been cut the edge of the liver turns back much more easily and the end of the ligament attached to the liver can be used as a tractor

Fig. 173.—Clamps on the suspensory ligament. The ligament can be cut between clamps for better exposure.

without traumatizing the tissue of the liver (Fig. 173). According to most anatomists, this ligament does not have the function of suspension. It can always be sutured or the ends tied together after the deep part of the operation is completed. In doing a cholecystectomy it is usually best to begin with the dissection of the cystic duct; with some thick-

walled gallbladders it may be better to begin at the fundus and dissect downward (Figs. 174 and 175).   Beginning at the cystic duct, it is best to dissect the lower end of the gallbladder and also the cystic duct away from the liver and common duct before clamping or tying; then the cystic duct and cystic artery can be clamped separately or at one time.

Fig. 174.—Suspensory ligament divided.   Dissection of the cystic duct from the liver, common and hepatic ducts, the gallbladder being held with the fingers.

In this way the control of these structures is much more accurate and there is no danger of traumatizing the common or hepatic duct.

From the foregoing the following conclusions seem indicated:

1. The systemic circulation is one of the most important, if not the most important, avenue through which infection reaches the gallbladder.

2. With the knowledge now at our command we were unable to recognize all cases of cholecystitis, even with the abdomen open.

3. The clinical history is a most important factor in determining
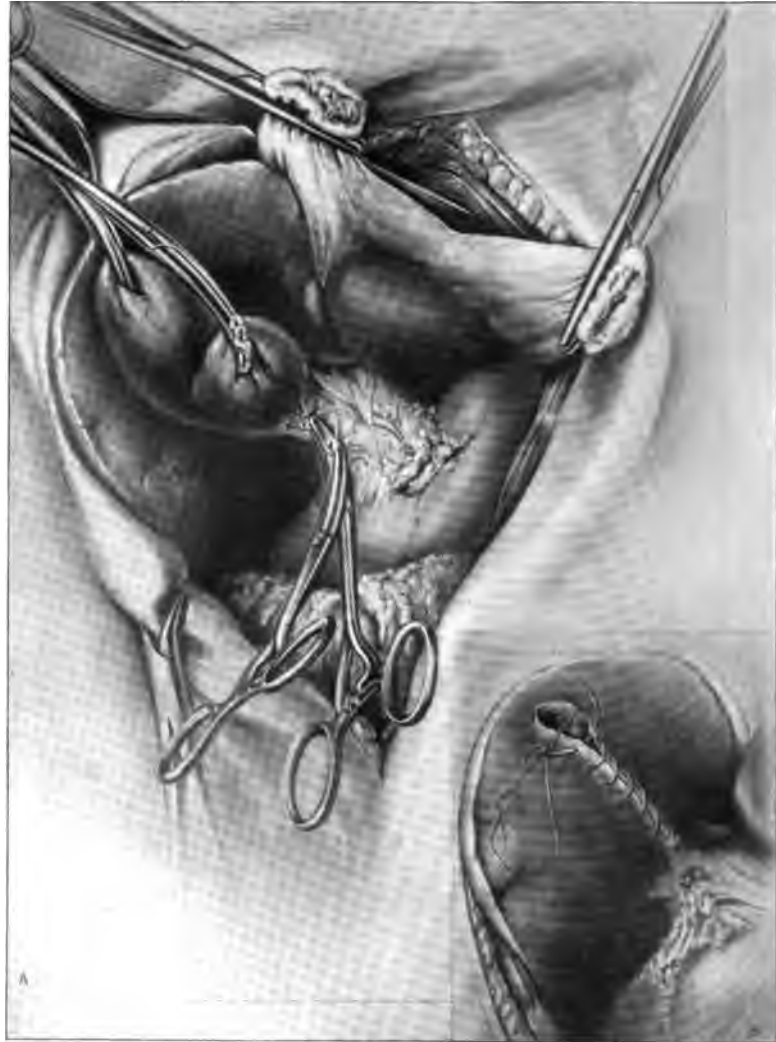
Fig. 175.—A, Cystic duct severed between clamps. Gallbladder turned back. One clamp under the cut-off end of the gallbladder catches any little vessels not included in the clamp on the cystic duct. B, Gallbladder dissected out in the usual way and fissure in the liver sutured.

the existence of cholecystitis. The significance of the enlargement of the regional lymphatics and the condition of the wall of the gallbladder are already recognized.

4. Chronic cholecystitis without stones does exist as a definite pathologic lesion, and produces symptoms that will be relieved by the removal of the gallbladder.   However, chronic cholecystitis may exist to a slight degree without producing definite symptoms.

5. The only change in the surrounding structures produced by the removal of the gallbladder is the dilatation of the common and hepatic ducts, and possibly the stump of the cystic duct.   Dilatation is apt to be most marked in the hepatic duct; it is least at the intestinal end of the duct.   Dilatation seems to stop where the duct passes through the muscle of the intestinal wall.

6. Eventually this dilatation, with increased pressure, overcomes the action of the sphincter at the intestinal end of the duct, and the bile passes through into the duodenum with very little resistance.   We believe that this mechanism explains why the removal of the gallbladder cures symptoms produced by inflammation of the pancreas, assuming that the inflammation in the pancreas is caused by bile from the common duct entering the pancreatic ducts.

7. The changes in the ducts which follow cholecystectomy indicate that the gallbladder has a definite function.

REFERENCES

1. Archibald, E.: "A New Factor in the Causation of Pancreatitis," presented at the Seventeenth Internat. Cong. Med., London, 1913.
2. Deaver, J. B., and Ashhurst, A. P. C.: "Surgery of the Upper Abdomen," Phila., Blakiston, 1913, vol. 2, p. 2.
3. Rosenow, E. C.: "Elective Localization of Streptococci," Jour. Amer. Med. Assoc., 1915, lxv, 1687–1691.
4. Mayo, C. H.: "Papillomata of the Gallbladder," Ann. Surg., 1915, lxii, 193–196.
5. Mayo, W. J., and Mayo, C. H.: "Surgery of the Liver, the Gallbladder and the Biliary Ducts," Keen's Surgery, Philadelphia, Saunders, 1908, vol. 3, p. 1006.
6. MacCarty, W. C.: "Pathology of the Gallbladder and Some Associated Lesions," Ann. Surg., 1910, li, 651–669.
7. Flexner, S.: "The Constituent of the Bile Causing Pancreatitis and the Effect of Colloids on its Action," Jour. Exper. Med., 1906, xiii, 167–177.
8. Oddi, R.: Di una speciale disposizione di sfintere allo sbocco del coledoco, Perugia, 1887; Monitore zoologico italiano, 1894, v.   Quoted by Luciani, L.: Human Physiology, London, Macmillan, 1913, vol. 2, pp. 214–217.
9. Opie, E. L.: "The Etiology of Acute Hemorrhagic Pancreatitis," Bull. Johns Hopkins Hosp., 1901, xii, 182–188. Diseases of the Pancreas, Philadelphia, Lippincott, 1903, p. 121.
10. Mayo, W. J.: "Cholecystitis Without Stones or Jaundice in its Relation to Chronic Pancreatitis," Amer. Jour. Med. Sic., 1914, cxlvii, 469–474.
11. Rost, F.: "Die funktionelle Bedeutung der Gallenblase.   Experimentelle und anatomische Untersuchungen nach Cholecystektomie," Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxvi, 710–770.
12. Deaver, J. B., and Pfeiffer, D. B.: "Chronic Pancreatitis," Ann. Surg., 1914, lix, 841–847.
13. Mayo, C. H.: "Cholecystostomy versus Cholecystectomy," Tr. South. Surg. and Gynec. Assn., 1915.

RUPTURE OF THE COMMON BILE-DUCT ASSO-CIATED WITH SUBPHRENIC ABSCESS*

HERMON C. BUMPUS, JR.

In a thorough review of the literature on ruptures of the common bile-duct I was able to bring to light but 7 cases besides the case reported herein.

Janeway,[1] in 1887, described a case which came to necropsy. A stone was found obstructing the common duct, causing suppuration, dilatation, and perforation of all three ducts. The pyloric end of the stomach, duodenum, and transverse colon were all adherent to the under surface of the liver. Upon removal of the liver a subdiaphragmatic abscess was discovered. The patient had given a history of a gall-stone colic of fourteen years' duration, with accompanying jaundice and the passing of calculi on several occasions. The terminal illness, a typical gall-stone attack, began one week before death. A very sharp abdominal pain occurred forty-eight hours before death, probably at the time of perforation.

McWilliams[2] collected and reviewed 114 cases of perforation of the biliary system, of which 4 were perforations of the common duct. One of them (Kehr's case) was that of a woman aged fifty-one years, who had had symptoms for four days, accompanied by jaundice. A cholecystectomy was done, but the patient died. Calculi in both the common and hepatic ducts and perforation of the common duct were found at necropsy. The second case, reported by Riedel, was that of a man aged fifty-six years, with symptoms of three days' duration. A cholecystostomy was done, but the patient did not recover. Necropsy revealed a calculus in the common duct with accompanying perforation. The third case was reported by Routier, and was that of a woman aged fifty-six years, with symptoms of only one day's duration. Operation revealed free bile and a perforation of the common duct. The gallbladder and peritoneal cavity were drained and the woman recovered. At a second operation (cholecystectomy) multiple stones in the gallbladder and ducts were found. The fourth of this group was Neupert's case: a woman aged forty-three years, with symptoms of fourteen hours'

duration, with jaundice. A rupture at the juncture of the cystic and common duct and an impacted stone in the common duct were found at operation (cholecystectomy). The patient made a complete recovery.

Campbell-Horsfall[3] has reported a case in detail. His patient, a woman aged forty-five years, suffered with dyspepsia and spasmodic epigastric pain for years. Following one of these attacks of unmistakable gall-stone colic she was seized with intense pain in the upper abdomen and chest. When first seen, she was in a state of complete collapse. Operation was performed the following day. On opening through a right rectus incision bile-stained fluid and pus welled up. The gallbladder was shrunken, and the fluid could be traced to the common duct. A rubber drain was carried down to the common duct and a cigarette drain placed in the right kidney pouch. The pelvis was also drained through a stab wound. Two weeks later an accumulation of biliary matter was drained through a second stab wound in the left flank. The patient made an uneventful recovery. Campbell-Horsfall feels that this case is of interest as demonstrating the urgency and success of early operation. He cites the four preceding cases and points out that in those reported by Riedel and Routier, in which operative procedures were instituted early, recovery resulted; the other two, in which operative procedures were delayed, ended fatally.

Lapenta[4] reports one case. A woman, aged sixty-nine years, was seized with excruciating epigastric pain, followed by vomiting and coma. There was no history of previous gall-stone attacks. At operation the following day the gallbladder was not distended. The lesser peritoneal cavity contained bile and bloody serum. There was a perforation 8 mm. in length in the common duct just below the entrance of the cystic duct from which a calculus was protruding. This and several smaller stones were extracted, a cholecystostomy being done. A cigarette drain was placed to the point of rupture. Recovery was uneventful. Lapenta lays great emphasis on the coma, believing it to be diagnostic of rupture of the common bile-duct. It is of interest in this connection to note that Campbell-Horsfall reports his patient as unconscious when first seen.

Meissner[5] has reported 12 cases, but all were traumatic in origin, and will not, therefore, be considered here.

The history of our own case is as follows:

Mrs. A. P., a married woman aged forty-four years, came to the Mayo Clinic January 24, 1916. Her family history was negative, and the only sicknesses she could recall, save those directly connected with her present trouble, were grip and tonsillitis, fourteen years before, and an occasional attack of rheumatism. She had been pregnant six times. Four children were living, the oldest twenty-four, the youngest seven.

Two were born before full term and lived but a few weeks. During her first pregnancy, twenty-four years before, she had several attacks of severe, cramp-like pain below the right costal margin. Two years later, during her second pregnancy, the severity and frequency of these attacks increased, and on several occasions were accompanied by jaundice requiring two to three weeks to clear. Six months after this pregnancy she had a very severe attack, with extremely deep jaundice. During her third and fourth pregnancies she had frequent recurrences of this trouble, and during her fifth pregnancy she had as many as nine to ten attacks of gall-stone colic. Since then, i. e., for the past fifteen years, although she has had frequent and varied attacks, they have never been accompanied by jaundice. On several occasions she has passed calculi by bowel. Three months previous to her present trouble she had an attack lasting twenty-four hours, during which she vomited a great deal of bile-stained material. On December 25, 1915, about seven o'clock in the evening, the patient experienced considerable upper abdominal discomfort. This became progressively worse, and at ten o'clock the pain was so severe that she took a quarter of a grain of morphin for relief. At first, as in all the previous attacks, the pain was felt along the right costal margin, radiating through to the right shoulder-blade. At six o'clock of the morning of the second day she was seized suddenly with a sharp pain in the right lower quadrant, so severe that in spite of the fact that she had taken another quarter of a grain of morphin, it forced her to cry out with every breath. During the night she had three bowel movements. The next morning, however, the family physician could not get any results, either gas or fecal, with enema. The low abdominal pain continued for two and one-half days. One week after the onset of the attack a severe burning pain developed in the base of the right chest and at the same time a swelling slowly appeared in the right lower quadrant. This continued to grow in size and her condition became worse until January 24, when she was examined in the Clinic.

The patient was emaciated and weak, requiring assistance to get about. A slight yellow tinge was noted in the sclera. Pulse, 120; temperature, 101° F. She had a short irritating cough and was unable to take a deep breath because of pain. The chest showed dulness and absence of breath-sounds at the right base. The abdomen was very tender and rigid over the region of the gallbladder. A large mass could be palpated below the right costal margin, extending along the nipple-line to the crest of the ilium. The urine was acid and contained a trace of albumin; specific gravity, 1017. White blood-cells, 17,600. Roentgenologist's report: Increased density in the lower right chest to the level of third rib in front. Diaphragm appeared to be above the mass.

Operation.—On January 26 a diagnosis of subdiaphragmatic abscess and acute inflammation of the gallbladder having been made, an operation was performed under local anesthesia (Judd). Temperature, 100.4° F.; pulse, 120. Through a stab incision in the right flank a

blunt dissection was made forward outside the peritoneum to the point of adhesion between the abscess mass and the abdominal wall. Through an opening here two to three quarts of turbid, greenish yellow, somewhat purulent, odorless fluid and numerous calculi escaped under considerable pressure. A large rubber-tube drain was inserted and the patient placed in bed. The abscess cavity drained biliary detritus for seven days; the temperature and pulse returned to normal. Although still quite weak, the patient was up on the tenth day and gained rapidly until the night of the thirteenth day, when she was seized with an attack of typical gall-stone colic. The pain, which was very severe, began below the right costal margin, radiated through to the back, and was accompanied by nausea and vomiting. Her condition showing no improvement the next day, February 10, a second operation was performed through a modified Bevan incision. There were many adhesions and the tissues were all very much indurated. The gallbladder was tense, cystic, and shrunken; the mucous membrane, though almost completely destroyed, still retained clear cystic fluid with numerous stones, but no bile. Some of the stones were impacted in the cystic duct, completely obstructing it. The abscess, which had been drained two weeks previously, was found to be subphrenic, there being a large pocket in the right anterior subphrenic space. With the operating field clear of old clots and adhesions, bile was found leaking from a point high on the common duct, just at the juncture with the cystic duct. There were also two stones obstructing the common duct, one stone presenting at the perforation.

Cholecystectomy and choledochotomy were done, and a Robson hepatic drain was placed in the common duct. The subphrenic abscess was well sponged out and packed with three strips of iodoform gauze and a split tube. A second split tube and gauze were placed so as to drain the stump of the cystic duct. The wound was closed in the usual manner, and before the patient was taken from the table bile was flowing freely from the Robson tube.

The patient's convalescence was uneventful, save during the third and fourth days, when nausea and vomiting were very annoying. Gastric lavage every six hours overcame this complication, although for several hours the pulse was 130. On the sixth day, while the gauze was being shortened, the Robson tube came out. All the gauze was removed on the eighth day, and the rubber tubes on the thirteenth and fourteenth days, respectively. At this time the patient was out of bed. Three days later, when she left the hospital, all bile drainage had ceased, although a small sinus persisted.

Moynihan[6] states that the cardinal symptoms of rupture of the common bile-duct are: Jaundice, absence of bile in the stool, gradual distention of the abdomen, and wasting. The jaundice, he points out,

'16—20

is never intense, but is rather a yellow tinge in the skin or a slight yellowing of the sclera, as in the case reported here. This is because the bile is only slightly absorbed by the peritoneum after the first inflammatory exudate is set up, and because there is no retention of it in the liver. For the same reason the bile in the urine is slight. The stools are always clay-colored, for all the bile escapes from the rupture, none entering the intestine. A constant feature is the gradual distention of the abdomen. This may be general, due to the flow of the bile over the entire abdominal cavity, but more commonly is confined to one part as a local swelling, generally in the right hypochondrium, as in our case. A rapid loss of flesh is always noted, and emaciation and weakness may be extreme; our patient lost 20 pounds in a little over two weeks. The typical pathologic condition is an inflammatory softening and distention of the walls, due to the obstruction of the duct with a final ulceration and giving way of the tissues. The rupture may occur into the general peritoneal cavity, but by the aid of protective adhesions a localized abscess is generally formed.

Riedel[7] reports two cases in which a localized abscess resulting from rupture of the cystic duct had involved and perforated the common duct.

The foregoing 8 cases follow closely the symptoms and pathology given by Moynihan. They also demonstrate the benefit to be derived from early operation, preferably in two stages. The first stage, which consists of drainage, enables the patient to undergo the second and more extensive operation with far less risk.

REFERENCES

1. Janeway, E. G.: New York Med. Jour., 1877, xxvi, 831. Quoted by Moynihan, *loc. cit.*
2. McWilliams, C. A.: "Acute Spontaneous Perforation of the Biliary System into the Free Peritoneal Cavity," Ann. Surg., 1912, lv, 235-263.
3. Campbell-Horsfall, C.: "A Case of Perforated Common Bile-duct Followed by Subphrenic Abscess, Operation and Recovery," Brit. Med. Jour., 1913, ii, 118-119.
4. Lapenta, V. A.: "Perforation at the Juncture of Cystic and Common Duct," Surg., Gynec. and Obst., 1915, xx, 552-553.
5. Meissner: "Die Zerreissungen der Gallenausführungsgänge durch stumpfe Gewalt," Beitr. z. klin. Chir., 1907, liv, 204-221.
6. Moynihan, B. G. A.: "Remarks Upon the Surgery of the Common Bile-duct," Lancet, 1906, i, 147-154.
7. Riedel: "Partielle oder totale Zerstörung von Ductus cysticus und choledochus durch Stein," München. med. Wchnschr., 1912, lix, 2403-2406.

LIFE EXPECTANCY FOLLOWING OPERATIONS ON THE GALLBLADDER*

CHARLES H. MAYO

No one more than you who are dealing with life statistics realizes the wonderful changes that are so rapidly occurring in the history of medicine; how within a matter of a few years we have gone from the extensive use of drugs back to the study of the living cell, the way in which nature deals with diseased organs and the individual cell as differentiated from general body symptoms which are secondary to the individual cell.

There is usually involvement of the tissues by bacteria in the conditions that cause our death, and while we cannot exist without bacteria, often we cannot live with them. The types of cells are very much alike, whether they are vegetable or animal. In the end all two-celled organisms come to natural death, regardless of their type.

Mortality alone has been too long considered to the exclusion of morbidity. We often find that general diseases and local diseases so injure a man as to make him a non-producer, even though he may live long. In such cases death is attributed eventually by your statistics to some other ailment, such as pancreatitis, cirrhosis of the liver, and diseases of the heart muscle or kidney. Diseases of the gallbladder are rarely given as the cause of death. The almost trivial disease conditions of life that impair health and are responsible for a low percentage of mortality only little above the average at the various ages for which statistics are compiled lead to a mortality which in the end is attributed to the wrong thing.

Therefore it would be an economic proposition for great life insurance companies to give all persons insured in their companies a free

examination—not treatment: merely to tell them of their condition so that they may remedy defects that otherwise would not be looked after. Many who regularly consult their dentist neglect to consult their family physician for fear of appearing to be unduly worried about themselves.

In the last century, as you know, many years have been added to the average length of human life. This average, however, has been brought up by saving more babies and bringing more people to middle age. We still cannot bring them to old age, and today many drop dead between the ages of fifty and sixty who were supposed to be in good health. In such cases death is due usually to disease of the heart, to blood-pressure, or to kidney changes—the many and various conditions that men may have without realizing that they are sick.

The greatest change has come in the last few years in the new knowledge that every form of local disease is instituted and developed by bacteria; that there is no such thing as primary neuritis, tic douloureux, sciatic rheumatism, herpes zoster, or myalgia. They can all be reproduced in a certain definite percentage by injecting animals with bacteria grown from those diseases in man. Our rheumatisms, our heart diseases, all endoarterial inflammations, acute or chronic, are due to bacterial toxemia or to bacterial existence. In infantile paralysis experimental research with animals has resulted in our finding the specific germ and being able today to bring about a degree of paralysis in animals which varies according to the virulence of the germ and the resistance of the animal.

We now know that bacteria pass into the duct circulation and into the tissues of the gallbladder. In operating we find papillary gallbladder, thick-walled gallbladders, degenerations of all types, including cancer. Only occasionally, in some of the acute, foul-smelling cases of cholecystitis, are the bacteria present in the bile in large numbers. The obstruction and stasis are due to bacteria in the wall which change the mucosa and render it stiff and unable to expand.

The gallbladder is absent also in the horse, elephant, rhinoceros, deer, and mouse, but these animals have a duct that works just as well. This duct is made up of connective and elastic muscular tissue and is lined by mucous membrane. It pumps in the same way as the gallbladder.

In the earlier days, when we did not know what would happen if we removed the gallbladder, we made every effort to save it. However, these conditions of the gallbladder are not often in themselves fatal.

The patients die of secondary degenerations. In many cases in which we formerly failed to take out the gallbladder, thinking it would be better to save it, we had to reoperate because of cholecystitis, and in a few cases, for recurring stones. In one-fourth of all people who have disease of the gallbladder cholecystitis is present without stones. Most pancreatitis is secondary to disease of the gallbladder.

During the eleven months from November 1, 1915, to October 1, 1916, 921 persons were operated on for gallbladder trouble and for stones in the common duct. The mortality in these cases was 3.04 per cent. In 43 the gallbladder was merely drained because, on account of age or pregnancy or some serious condition, it was thought inadvisable to remove it. Among these the mortality was 14 per cent., one-half of which was for cancer. During the same eleven months the mortality from 719 cases of cholecystectomy was 1.8 per cent.

Accordingly, we conclude that a man without a gallbladder is in better average condition of health at the end of one year from the time of the removal of the gallbladder than a man who has a diseased gall-bladder, just as a man is a better risk without a diseased tonsil that may be the cause of heart disease, myocarditis, chronic kidney disease, and other conditions.

THE GEOGRAPHIC DISTRIBUTION OF AMEBIASIS*

ARTHUR H. SANFORD

"Tropical dysentery" of amebic origin has for years been known as a troublesome disease in our southern States. That it is not uncommon in regions with colder climates is not so well recognized, although sporadic cases have been reported in all parts of the world. To be sure, the disease is more severe and more frequent in the tropics and in subtropical climates, but a collection of cases reported in the north temperate zone leads us to state that amebiasis is a surprisingly widespread infection.

The classic report of Lösch[1] (1875) recorded the case of a patient with amebic dysentery at St. Petersburg, Russia. In England, Saundby and Miller[2] reported a case in the Birmingham district. The patient, who had never been away from that particular region, had ulcerative colitis and a liver abscess in which amebas were found. Saundby and Miller believe that theirs is the first case reported in which the patient contracted the disease spontaneously in England, and are inclined to think that the organisms are being brought to the British Isles by soldiers from the tropics. They call attention in their paper to the report by Juergens in regard to the occurrence of the disease in Berlin, and also to the fact that Caussade and Joltrain recorded one case from Paris, and Kartulis (1906) stated that Scandinavia, Great Britain, Spain, and Portugal were the only European countries from which amebic dysentery had not been reported. Low,[3] among others, has recently reported many patients coming to London from Gallipoli. In the Paris letter[4] to The Journal of the American Medical Association, dated March 24, 1914, it is stated that:

"Dean Landouzy, of the Faculté de médecine de Paris, drew the

attention of the Académie de médecine to the importation into Europe, especially France, of amebic dysentery by carriers. He reported the case of a patient who died of a large abscess of the liver due to amebic dysentery which was unrecognized, partly because the symptoms were obscure, and partly because the patient had never left the north of France. This patient, therefore, had been infected in France in some as yet unknown manner. Other cases of the same kind have already been reported in France in the last ten years, and there is no doubt that amebic dysentery is being imported into the country."

Albu[5] reported true amebic dysentery in a young German woman after a trip to Silesia and Breslau.

On our own continent many interesting reports have been made of cases in temperate climates. In 1902, Dock[6] reported typical amebic dysentery in a patient who had never been out of the State of Michigan or in contact with a case from the South. In the discussion of this paper Walsh reported two patients seen in New York City, and Libman, ten cases of amebic liver abscess, also in New York. None of these patients had resided outside of New York City.

The disease is rather common in Maryland, which, of course, is in the zone in which it is commonly believed to occur. However, in discussing the cases of the previous fourteen years which were observed in Johns Hopkins Hospital, Futcher[7] says: "'Tropical dysentery' is a misnomer. Amebic dysentery is not confined to the tropics, but often originates in the subtropical, even in the higher, zones. Sporadic cases occur in New England."

The next year Tuttle[8] called attention to the fact that it should not be called a "tropical disease," and reported 3 patients who had never been more than 50 miles south of New York, and 15 patients who had always resided north of 37° latitude.

Patterson,[9] in 1910, reported a case endemic in New York, and stated that he had had 3 others. He also reported 15 from the literature. "A study of these cases does much to disabuse one of the idea that amebic dysentery is exclusively a tropical disease."

One of the most interesting reports is that of Axtell.[10] He had a patient who had been a mate on a government boat on the Tanana and Yukon Rivers, Alaska. This man supposedly contracted amebic dysentery by drinking swamp water in the spring. Amœba coli was found, and amebic ulcerations were seen with the proctoscope. The man claimed that he knew of 13 or 14 others with the same trouble.

A large group of cases was reported by Rosenberger.[11] Examina-

tions were made of the stools of the patients in a hospital for the insane in Philadelphia. Of 137 males, 112 had amebas, and of 141 females, 86 showed the parasites. The author calls them all Amoeba coli, and says that the patients were constipated and not dysenteric.

It is scarcely necessary to quote other reports of sporadic cases in order to add weight to the statement that persons with this disease are not so uncommon in the northern States.

For several years at the Mayo Clinic the stools of patients with chronic diarrhea have been systematically examined. Sistrunk,[12] Giffin,[13] and I[14] have all made reports of these findings. During the past five years there have been approximately 6500 stool examinations. Repeated examinations, and examinations for occult blood, etc., reduce the number of patients examined for parasites to about 5000. The same method has been used for all these patients. One-half ounce to an ounce of Epsom salts is taken before breakfast. The patient eats his breakfast and comes to the laboratory for the passage of his stool. This is examined at once. A cover-slip preparation is made and the slide kept at body temperature by means of a warm stage. It should be mentioned that after the administration of castor oil stools are unsatisfactory for microscopic examination.

In classifying the amebas found in fresh specimens, we have followed Craig's[15] descriptions, noting especially the appearance of the ectoplasm, the nucleus, its position, etc., the motility and the pseudopodia, whether there is mere bulging of the ectoplasm, or lobose and finger-like prolongations, and especially whether the organisms are ingesting and digesting red blood-cells. The color, which at times is noticeably green in some organisms, is thought by some observers to be due to digestion of red blood-cells.

In some instances we have stained specimens with iron hematoxylin, following in detail, both in the preparation and in the study of the specimens, the valuable monographs of James[16] and of Craig.[15] By this method we are able to examine especially the nuclear structures. In Endamoeba histolytica the beaded arrangement of chromatin around the outer portion of the nucleus, the reticulated nucleoplasm, and the sharp karyosome surrounded by a clear zone are all characteristic. In the non-pathogenic ameba Endamoeba coli, the chromatin is seen as a heavily staining mass, forming the karyosome, and as a dense ring about the outer portion of the nucleus.

We have not been able to study as fully as we would like the various

phases in the processes of reproduction of these organisms. Rather frequently, however, we see cysts with only four daughter-cells—the tetragena, or histolytica cyst, and again those of Endamœba coli with eight nuclear bodies. Many protozoölogists claim that an absolute diagnosis can be made only by studying cysts. We have recognized fully the difficulties in attempting to classify types of amebas, and feel that in some instances errors in diagnosis readily occur.

There have been 284 patients from northern States in whom we have reported Endamœba coli, the supposedly non-pathogenic organism, and 535 patients from the same sections of the country who were infected with organisms classified as Endamœba histolytica.* In all there were 819 persons in whose stools we found some type of ameba. The majority of these patients were natives of the State in which they resided, and all of them became infected while living in the northern portions of the tem perate zone. It is also not conceivable that many, if any, of these patients could have contracted the disease by contact with persons from the South or tropics. A consideration of the number of patients with amebas from the various States is of interest (see table and map). Besides the northern cases, we have as "controls" 95 patients from the South or the Orient in whom we have found amebas. Sixty-five of these have Endamœba histolytica, and 30, Endamœba coli, so that in all the 5000 patients examined for parasites amebas of some sort were found in 18 per cent. It should be remembered, however, that the number having stool examinations was less than 5 per cent. of the total number of patients registered at the Clinic during these five years.

When the complaints of these persons are considered, interesting facts are brought forth regarding symptoms in patients infected with amebas in temperate climates. Forty-one per cent. have constant diarrhea, and 33 per cent. have intermittent diarrhea, often alternating with periods of constipation; while nearly 26 per cent. have never had any bowel trouble except constipation. Occasionally these patients have ulcerations that are seen with the proctoscope, but the majority of examinations of this sort are negative. In fact, the entire syndrome is not so severe in the average ameba-infected patient of the North as it is in those of the South or tropics.

The question arises as to the significance of pathogenic amebas in the stools of patients who have never had diarrhea. It would certainly

* All organisms formerly reported as Endamœba tetragena are now grouped with Endamœba histolytica.[17,18]
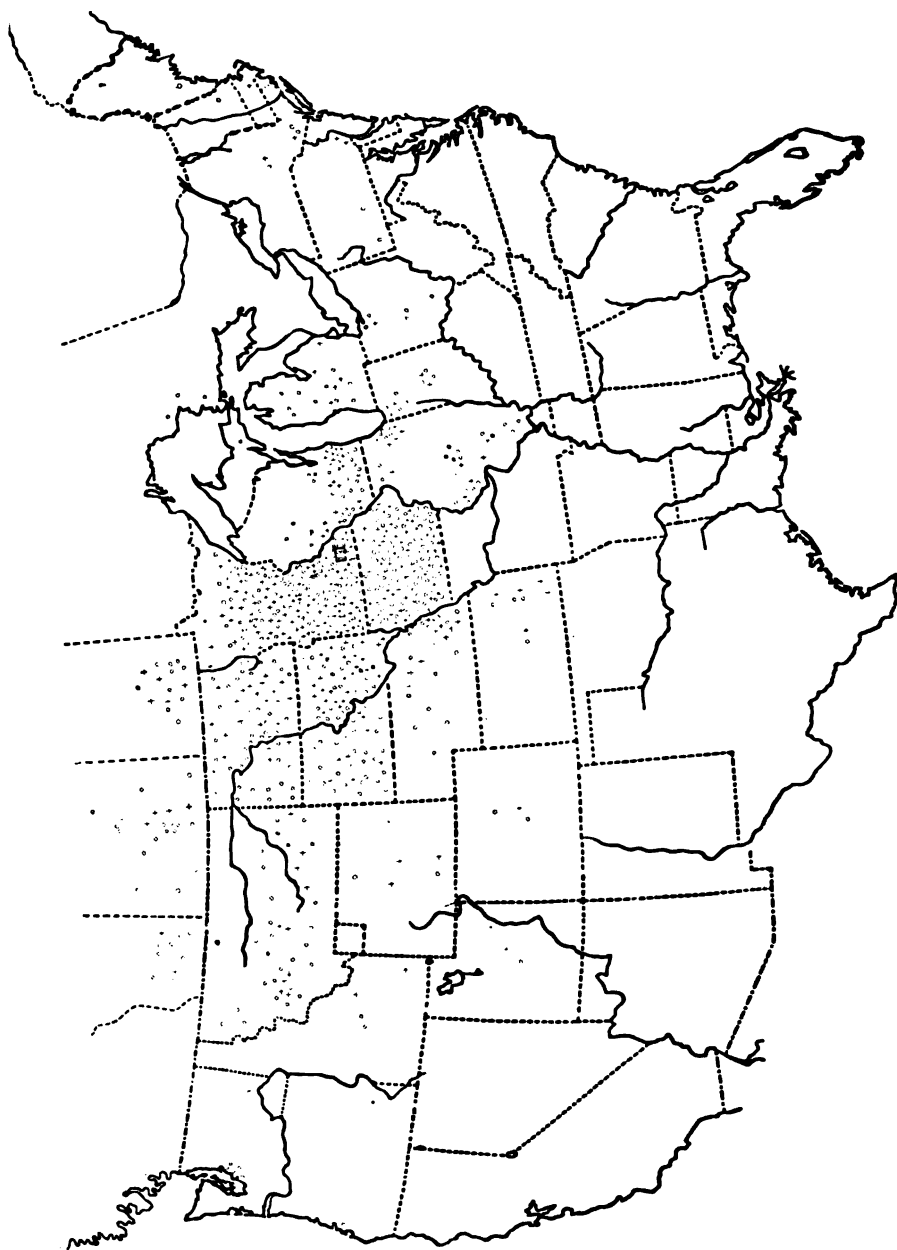
Fig. 176.— Patients developing amebiasis in northern United States and Canada examined at the Mayo Clinic, 1911-1916; ∗, Endamoeba histolytica; ⊙, Endamoeba coli.

CASES OF AMEBIASIS

NORTHERN STATES AND CANADA	Constant diarrhea: Endamœba histolytica	Endamœba coli	Intermittent diarrhea: Endamœba histolytica	Endamœba coli	Constipation: Endamœba histolytica	Endamœba coli	Total Endamœba histolytica	Total Endamœba coli	Total amebas
Minnesota	51	34	38	33	44	29	133	96	229
Iowa	41	10	42	15	30	27	113	52	165
South Dakota	30	8	23	9	5	15	58	32	90
North Dakota	25	5	8	4	10	12	43	21	64
Wisconsin	16	3	11	6	8	4	35	13	48
Illinois	8	1	7	2	9	8	24	11	35
Michigan	6	0	4	1	1	4	11	5	16
Indiana	1	1	4	3	2	0	7	4	11
Ohio	2	1	0	1	2	0	4	2	6
Kansas	1	1	3	2	0	2	4	5	9
Nebraska	9	2	3	4	4	3	16	9	25
Wyoming	1	1	1	0	0	2	2	3	5
Colorado	1	0	1	0	0	1	2	1	3
Montana	8	3	12	4	7	3	27	10	37
Idaho	1	1	1	0	0	1	2	2	4
Utah	1	0	1	0	0	0	1	1	2
Oregon	1	0	1	0	0	1	1	1	2
Washington	2	0	3	0	1	0	6	0	6
New York	1	0	0	1	1	2	3	2	5
Pennsylvania	1	1	0	1	0	0	2	2	4
Massachusetts	0	1	0	0	1	0	0	1	1
New Hampshire	0	0	0	0	0	1	1	0	1
Maine	1	0	0	0	0	0	1	0	1
Saskatchewan	8	0	6	2	4	2	18	4	22
Manitoba	5	1	3	3	2	2	10	5	15
Alberta	3	0	2	1	3	1	8	2	10
Ontario	1	0	2	0	0	0	3	0	3
Totals from North	224	75	175	92	136	117	535	284	819
Total Number of Patients, 1911–1916	90	4	90	12	25	14	65	30	95
Southern States and Tropics	…	…	…	…	…	…	600	314	914

seem that these patients were not in need of immediate treatment. However, it must be remembered that in the South and tropics liver abscesses of amebic origin may occur in just this type of patient. Jones[19] has said: "Amebiasis may exist in a mild form or even advanced form without dysentery." He reports five cases of amebic abscess, in four of which no history of dysentery was given.

In a recent editorial [20] is found the following statement: "The recognized existence of unharmed or immune carriers of other types of organisms makes it seem less strange today than it might have seemed a few years ago to learn that there are some individuals apparently perfectly healthy who harbor amebas in large numbers for long periods without any unfavorable symptoms."

These carriers may be a source of danger to others, and in themselves may be considered potential dysentery patients. Regarding treatment of such patients, Phillips[21] has said, "All carriers, even though they may have never had dysenteric or other symptoms, are to be considered as cases of amebiasis and treated as such." Many of our patients of this kind, as well as those with active symptoms, have been treated with emetin hypodermically, ipecac by mouth, and kerosene enemas.*

We are often asked for an explanation of the source of the infection. The soldier returning from the tropics surely cannot be held entirely responsible for the spread of the disease, as the majority of our patients have come from rural communities and have never come in contact with persons with tropical infections.

We have considered the question of water supply in our series of more than 900 patients with endamebas, including those from the South and the Orient. Forty per cent. stated that their water supply was from a source that might be suspected; namely, shallow wells, lakes, springs, cisterns, reservoirs, streams, and in a few instances even ditches. On the other hand, 60 per cent. of the patients harboring these parasites affirmed that the source of their water supply was good—deep wells, many of them of the artesian type. It has been suggested that fruits and green vegetables shipped from the South and handled there by carriers of amebas may be the means of spreading the disease northward. But here again we cannot imagine that the northern farmer will indulge frequently his desire for out-of-season strawberries and lettuce when he himself may raise them for market. It is known that some of the do-

* A more detailed study of symptomatology and the effects of treatment of amebiasis in northern patients is to be undertaken at another time.

mestic animals, horses, for instance, may be infected with amebas, and Lynch[22] has shown that the rat, Mus norvegicus, suffers from spontaneous amebic dysentery similar to that occurring in man, the amebas in its stools resembling Endamœba histolytica. Furthermore, Lynch has proved definitely that typical dysentery can be produced experimentally in the rat with amebas from man. In conclusion he states that the rat is a possible or probable disseminator of dysenteric amebas pathogenic for man.

We have undertaken the transmission of amebas from man to animals in a few instances. When old cats were used we did not meet with success. However, in a small series we have infected kittens, using the technic of Baetjer and Sellards[23] for intracecal injections. These animals developed dysentery in from six to ten days, with amebas in their stools.

It is not in the province of this paper to discuss the question of specific pathogenicity of amebas. It is agreed now that the parasitic types have never been cultivated even in mixed culture with bacteria. Accordingly, the first of Koch's postulates has not as yet been met. The question as to whether symbiosis plays a part in the disease is pertinent and difficult to answer. There are many problems yet to be solved in connection with this subject, and there is a field for study in the North as well as the tropics.

In conclusion, I would reiterate that it should be realized that this infection is general and that stool examinations are worth while for any patient with vague abdominal complaints or chronic diarrhea, no matter whence he comes.

REFERENCES

1. Lösch, F.: "Massenhafte Entwickelung von Amöben im Dickdarm," Virchow's Arch. f. path. Anat., 1875, lxv, 196–211.
2. Saundby, R., and Miller, J.: "Amœbic Dysentery with Abscess of the Liver," Brit. Med. Jour., 1909, i, 771–773.
3. Low, G. C.: "The Treatment of Amœbic Dysentery," Brit. Med. Jour., 1915, ii, 714–716.
4. Paris letter. Jour. Amer. Med. Assoc., 1914, lxii, 1267.
5. Albu, A.: "Zur Kenntniss der sporadischen einheimischen Dysenteria," Ztschr. f. klin. Med., 1905, lvi, 432–448.
6. Dock, G.: "Amebic Dysentery in Michigan," Jour. Amer. Med. Assoc., 1902, xxxix, 617–620.
7. Futcher, T. B.: "A Study of the Cases of Amebic Dysentery Occurring at the Johns Hopkins Hospital," Jour. Amer. Med. Assoc., 1903, xli, 480–488.
8. Tuttle, J. P.: "Amebic Dysentery: Its Local Lesions and Treatment," Jour. Amer. Med. Assoc., 1904, xliii, 1022–1027.
9. Patterson, H. S.: "Amebic Dysentery in New York," Med. Rec., 1910, lxxvii, 835–836.
10. Axtell, W. H.: "Amebic Dysentery Contracted in the Arctics of Alaska: Report of a Case," Northwest Med., 1911, n. s., iii, 51.

11. Rosenberger, R. C., and Terrell, T. C.: "Amebiasis and the Results of Tests for the Determination of Occult Blood in the Feces," New York Med. Jour., 1913, xcvii, 62–64.
12. Sistrunk, W. E.: "Intestinal Parasites Found in Individuals Residing in the Northwest," Jour. Amer. Med. Assoc., 1911, lvii, 1507–1509.
13. Giffin, H. Z.: "Clinical Notes on Patients from the Middle Northwest Infected with Entamebas," Jour. Amer. Med. Assoc., 1913, lxi, 675–678.
14. Sanford, A. H.: "Intestinal Parasites of Minnesota," Journal-Lancet, 1914, xxxiv, 335–338.
15. Craig, C. F.: "The Parasitic Amœbæ of Man," Philadelphia, Lippincott, 1911.
16. James, W. M.: "A Study of the Entamœbæ of Man in the Panama Canal Zone," Ann. Trop. Med. and Parasitol., 1914, viii, 133–320.
17. Craig, C. F.: "The Differential Diagnosis of the Intestinal Entamebas of Man," Arch. Int. Med., 1914, xiii, 917–944.
18. Darling, S. T.: "Budding and Other Forms in Trophozoites of Entamœba Tetragena," Arch. Int. Med., 1913, xi, 495–506.
19. Jones, G. I.: "The Treatment of Intestinal Amebiasis," Jour. Amer. Med. Assoc., 1915, lxiv, 982–983.
20. Craigiasis (Editorial) Jour. Amer. Med. Assoc.,1915, lxv, 1648–1649.
21. Phillips, L.: "Is Emetin Sufficient to Bring About a Radical Cure in Amœbiasis?" Brit. Med. Jour., 1914, ii, 1061.
22. Lynch, K. M.: "The Rat a Carrier of a Dysenteric Ameba," Jour. Amer. Med. Assoc., 1915, lxv, 2232–2234.
23. Baetjer, W. A., and Sellards, A. W.: "Continuous Propagation of Amœbic Dysentery in Animals," Bull. Johns Hopkins Hosp., 1914, xxv, 165–173.

THE CHOICE OF OPERATIVE PROCEDURE IN CANCER OF THE RECTUM AND PELVIC COLON *

CHARLES H. MAYO

One of the most serious, as well as one of the most interesting, surgical problems is the choice of methods in dealing with cancer of the rectum. It is serious because, when unrelieved, the disease leads surely to slow death, usually accompanied by much suffering. It is interesting because so many considerations are involved which influence the decision as to whether any operation is indicated, either palliative or radical, and if so, what. The first of these considerations is the location of the area involved by the cancer and the forms of the metastases; the second is the extent of the local disease and the associated local or general disease. Obesity increases the risk. The decision as to a palliative or radical operation will be influenced also by freedom from contact dissemination or grafts at a distance within the abdomen.

The intelligent patient usually inquires whether there is any other way of treating the disease than by surgery. If not, he wishes to know the operative risk and the prospects of cure; whether he will retain control of his bowels, and whether the new opening will be behind or in front. Among other therapeutic methods the use of radium is making great strides in the treatment of cancer, but at the present time it is limited to particular cases of local involvement, or to inoperable conditions. Radium treatment can hardly be classified in elective cases as being in any way in competition with the surgical treatment of cancer of the rectum except for epithelioma of the anus.

Operability.—Operability is a most important question. If the operability is high in a given clinic, the mortality will be high. The reverse is true of a low operability, for if only the best cases are selected for operation, the risk will be less. In order that the student may judge operative results all statistical reports must include a statement regard-

ing the operability. Cripps performed radical operations for cancer of the rectum on only 107 of 425 cases, an operability of 25 per cent. In the five years preceding 1916 our total operability was 53 per cent., but in the last three years it rose to 71.8 per cent., indicating that a chance for cure is now being given to a larger percentage of patients with this otherwise hopeless condition than formerly. That the operation is becoming more extensive is shown by the fact that in 6 cases we have performed, in addition, a total hysterectomy; in 12 cases we removed the posterior wall of the vagina; in 6 cases the posterior wall of the bladder; in 11 cases a part or all of the prostate, with one or both seminal vesicles; and in 6 cases one or more coils of small intestine. All of these procedures were necessitated by contact extension of the disease.

Mortality.—Of 753 patients in our clinic, a radical operation was performed on 430, with a general operative mortality of 15.5 per cent. Before 1910 the operative mortality was 17.8 per cent. From 1910 to 1913 it was 17.7 per cent., the operability being 51 per cent. In this earlier period a higher percentage of cases were seen late. Even at the present time 14 per cent. of the patients with cancer of the rectum observed have not had a complete physical examination, although they have been under treatment elsewhere, and some have even been recently operated on for hemorrhoids. In 1913, 1914, and 1915 the mortality was reduced to 12.5 per cent.; the operability was raised to 71.8 per cent., and the operative efforts were more radical.

Judging from the character of the colonic contents it would seem that the lymphatic system of the large bowel is very inactive—very much less active than that of the small intestine. For this reason cancer remains a local disease for comparatively long periods of time. That metastasis through the lymphatics is somewhat modified also by age is evident from the fact that in old people cancer remains a local disease longer than in young people. In a considerable number of necropsies performed on persons who have died from cancer of the rectum without operation it is found that there was little or no glandular involvement, death having been caused by perforation, peritonitis, or obstruction. The question as to operability and probable operative risk can often be answered by a general examination. In many cases, however, it is necessary to make an abdominal exploration to determine the advisability of a radical operation.

Prognosis.—Of the number of patients operated on, none less than three years ago, one-third lived three years or more and 28.3 lived five

years or more. By subtracting the natural death rate for the age period and the number of years, these percentages become respectively 37.5 and 35.8 per cent. Greater knowledge of the disease by the public will improve the present statistics for both the mortality and the cure.

The question of control of the bowels must be considered from several standpoints. Colostomies and uncontrolled intestinal openings for the escape of feces, whether they are abdominal or perineal, are much alike if the sigmoid loop is destroyed in making the new opening. As the left side of the colon is largely muscular and there is no impediment to the discharge of bowel contents after they have passed the splenic flexure, the patient with no anal control and with the sigmoid loop eliminated is much better off with an abdominal than with a perineal anus. If with loss of the anus the sigmoid loop can be retained, the control will be fair, except in case of loose bowel movements. Gas, however, is not controlled. If the cancer is low and the patient is obese, or there are other special reasons, a perineal operation may be chosen without abdominal exploration. With modern technic, however, various forms of abdominal colostomy are possible by which a very fair degree of control can be maintained and abdominal exploration permitted. Undoubtedly a considerable percentage of the Kraske operations done without abdominal exploration were on patients who had no possibility of cure because of internal metastases. Also much of the failure as to permanency of cure by the operations of earlier days was due to lack of exploration and to extraordinary efforts to preserve the normal or posterior location of the anus. Before 1900 the mortality was approximately 20 per cent., with more than 90 per cent. of recurrence. We believe that much of the progress in the surgery of cancer of the rectum has come from abdominal exploration and the abdominal colostomy with the sacrifice of a large area *en bloc* of the diseased bowel. The main purpose of the operation being to cure, the best results are secured when unhampered by any special effort to reëstablish the normal control of the anal outlet, except when it is indicated by reason of the location of the cancer. While the union of resected intestine within the abdomen is not followed by stricture, that effected outside of the peritoneal lined abdomen is practically always followed by stricture, and will usually necessitate some form of colostomy after much effort to maintain the lumen. This is the more true if there is good control of the anal sphincter and the less true if the sphincter is paralyzed. As to the extent of bowel to be removed, Fagge shows that the disease may extend two inches

'16—21

lower than the apparent growth, while according to Handley it can be
found microscopically more than double that distance above the manifest
disease. Such, however, are advanced cases, and each individual case
must be dealt with on its own merits. In the surgical treatment of
malignancy modern progress has been made by earlier diagnosis and
increasingly radical operations. Local recurrence calls for exploration.

The term "rectal cancer" is applied to such growths as are found
anywhere between the anus and the lower sigmoid. On anatomic
grounds the first inch and a quarter is the anal canal that is lined with
pavement epithelium. About 6 per cent. of cancers of the rectum are
found in this area. Here appear the epitheliomas and extensions of
adenocarcinoma from the lower rectum. Very early local epithelioma
may be successfully treated by local excision or destruction by cautery.
More extensive disease necessitates the Cripps operation of excision of
the anus, which should also include the removal of the inguinal glands,
this region having a double lymphatic return. From the anal canal to
the peritoneal-covered intestine is the lower rectum, in which are found
24 per cent. of the malignant growths of the region, usually adenocarci-
nomas, the common form of rectal cancer. The Cripps, Quénu-Tuttle,
and Hartmann operations, with or without the removal of the coccyx,
have been the common operative procedures, the upper rectum at times
being drawn through the mucosa-denuded anal canal, to be sutured out-
side for maintenance of the normal position of outlet, or more commonly
brought to the surface at the former position of the coccyx.

The upper rectum extends to the rectosigmoid juncture opposite the
third sacral vertebra. The Kraske procedure involves more extensive
removal of the lower sacrum with the coccyx, a higher placement of the
terminal bowel, and a more extensive removal of the rectum. Operation
for cancer of the rectum and rectosigmoid should be made by the two-
stage interval operation. If, by abdominal procedure, the division of
bowel below the growth can be made at a point which will leave at
least one-half inch or more of peritoneal-covered rectum within the cul-de-
sac, and the area of the disease to be removed is not too great to prevent
coaptation of the divided ends of the bowel, a tube resection can be done
with preservation of the control of the anal outlet as a one-stage pro-
cedure. A large rubber tube with a one-half-inch lumen is inserted
into the terminal proximal opening of the intestine and attached to it
by a purse-string suture. The tube is now passed into the rectum from
above and out of the anus. As the bowel ends approximate they are

sutured, and the tube, being further drawn upon, enfolds the suture line into the rectum. A second row of sutures is then applied, and upon
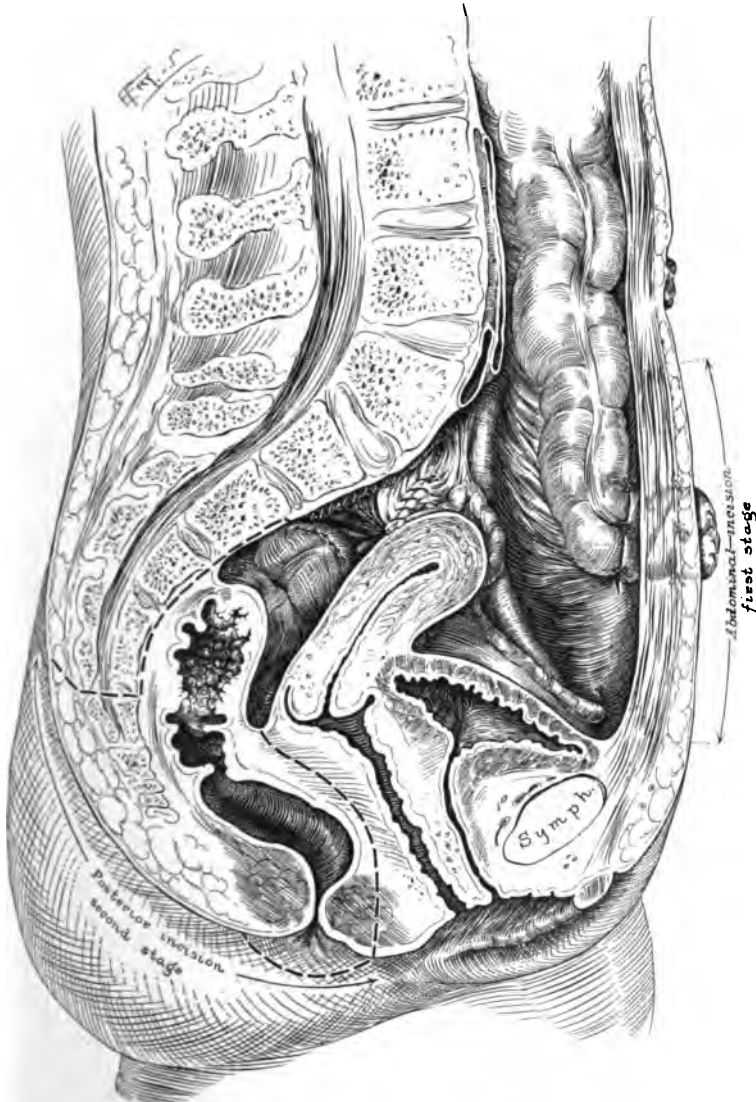
Fig. 177.—First stage: closure of pelvic brim by utilizing the uterus and broad ligaments. The Gersuny twist colostomy made one and one-quarter inches from the median line. Dotted lines indicate the extent of dissection for second stage.

further traction a third row of sutures. All intestinal contents are passed through the tube and in no way come in contact with the suture

line. The anal sphincter is temporarily relaxed by dividing it an-
teriorly with the cautery. The tube is sutured with catgut to the anus
and its position maintained for one week.

Cancer of the rectum and rectosigmoid which cannot be radically
removed with the preservation of the peritoneal-covered distal bowel
is best treated by a two-stage operation as follows: First, a midline in-
cision, exploration, division of the sigmoid above the growth, both ends
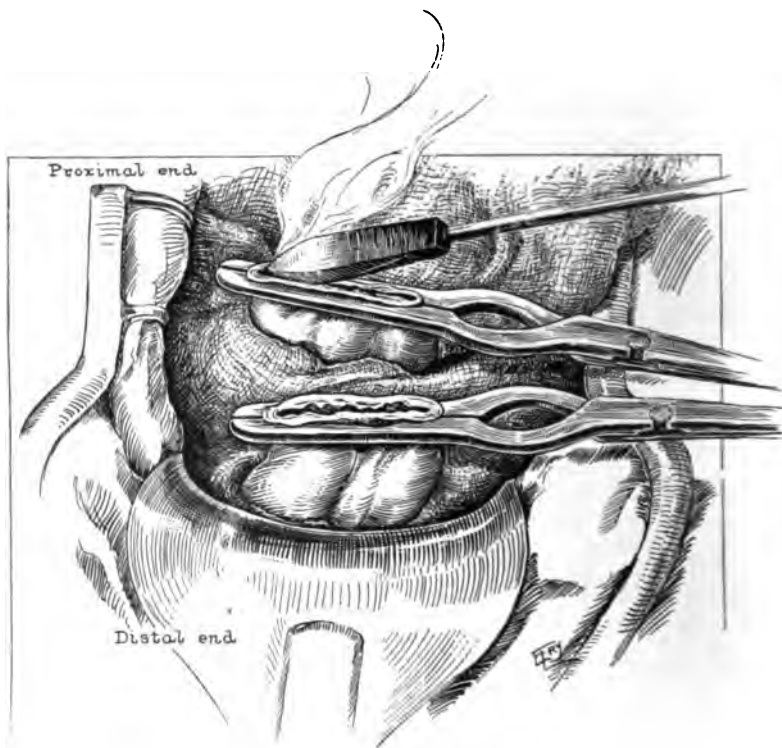
Fig. 178.—Division of sigmoid. Cautery sterilizing, before closing open ends.

turned in, the mesentery of the lower end ligated and separated from the
sacrum downward, and the distal end of the bowel turned into the cul-
de-sac beside the growth (Figs. 177, 178, and 179). The brim of the
pelvis is then closed off by peritoneal suture the back of the bladder,
the fundus of the uterus, the broad ligaments—any or all of the ad-
jacent peritoneal folds—being used to inclose the cancer and distal bowel
in the closed cavity of the pelvis (Figs. 180 and 181). Through a two-
inch incision to the left of the midline through the rectus and the entire

thickness of the abdominal wall the proximal closed end of bowel is drawn and sutured to the peritoneum and transversalis fascia from the inside of the abdomen.   It should project an inch and a half above the
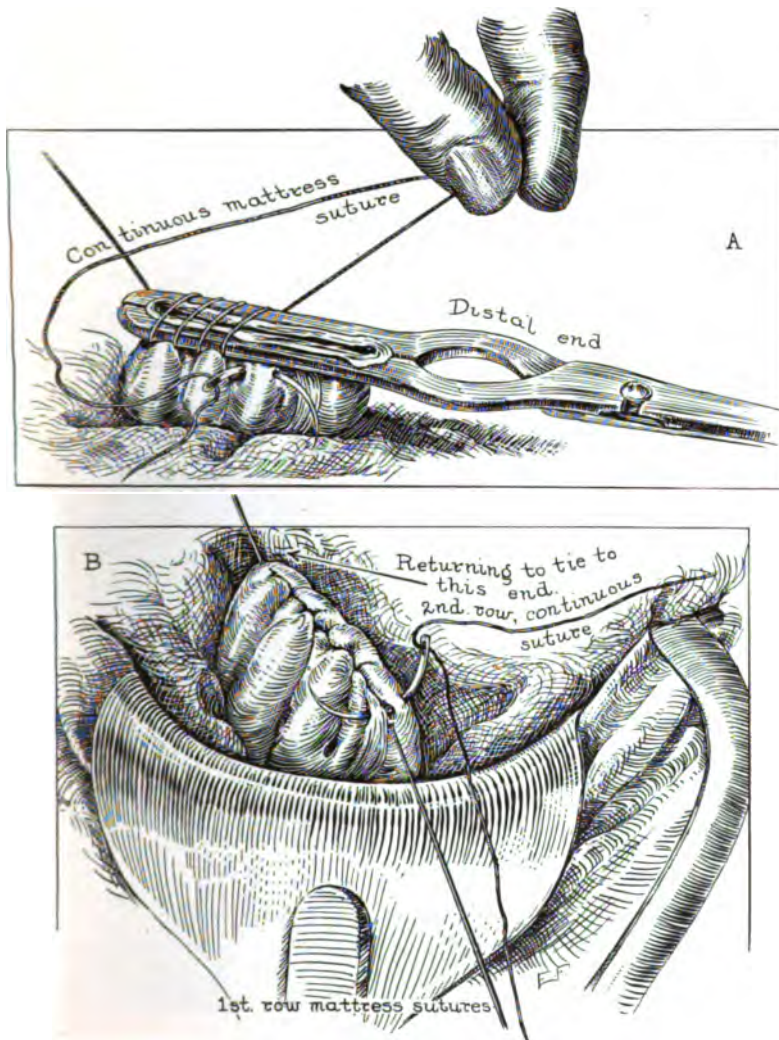
Fig. 179.—.1, Application of continuous chromic catgut suture for closing end of bowel; B, beginning of second row, continuous suture, for completion of closure of bowel.

skin. The projecting stump is twisted three-fourths to one turn, and pushed down and sutured around its upper border to the aponeurosis. Thus are created spiral valves and accordion plaiting within the thick-

ness of the rectus muscle, over which a belt gives very efficient control. The principle was devised by Gersuny long ago for posterior perineal surgery and was applied to the abdomen by Lilienthal. The second

Fig. 180. —Inturned ends of colon and beginning of suture which separates pelvis from abdominal cavity.

stage of the operation is done at the end of six days. A perineal incision is made, the anus closed, and a Kraske resection of the lower sacrum with removal of the coccyx and total removal of the rectosigmoid and rectum, including the anus, is done (Figs. 182 and 183). In six days the devita-

lized tissue is easily separated from its surroundings.   In eight or ten days a slough has usually developed through leakage of the intestine or infection from the cancer.
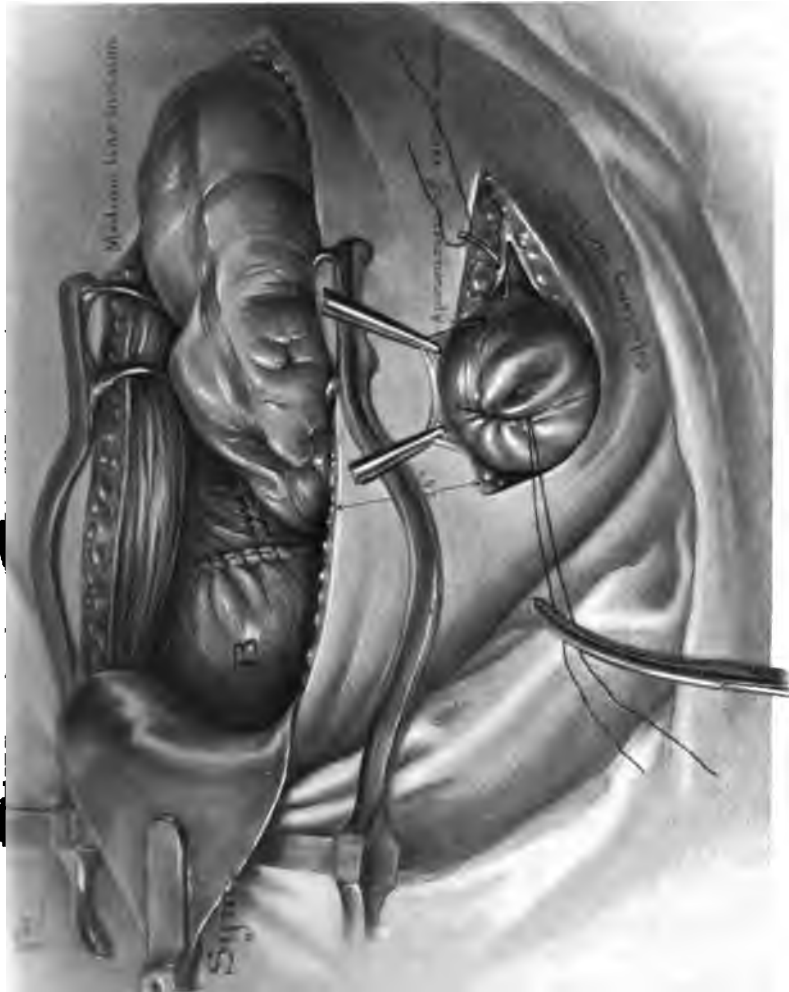
Fig. 181.- Seen through the large incision is the peritoneal closure of pelvic brim.   Suturing of proximal end to aponeurosis of rectus muscle, small incision.

When the growth is not too great to prevent the passage of a tube to invert the upper rectum through the growth, the Coffey procedure of inverting the upper portion of distal bowel through the cancer area and

out of the anus may be followed as a two-stage operation. We have employed this method with success, and Coffey had only 1 death in 8 cases.

Cancer of the lower sigmoid extending nearly to the rectosigmoid is well treated by the Mikulicz method, separation of the mesentery, and elevation of the diseased loop through the exploratory incision to a position above the abdomen. The sides of the intestine being first
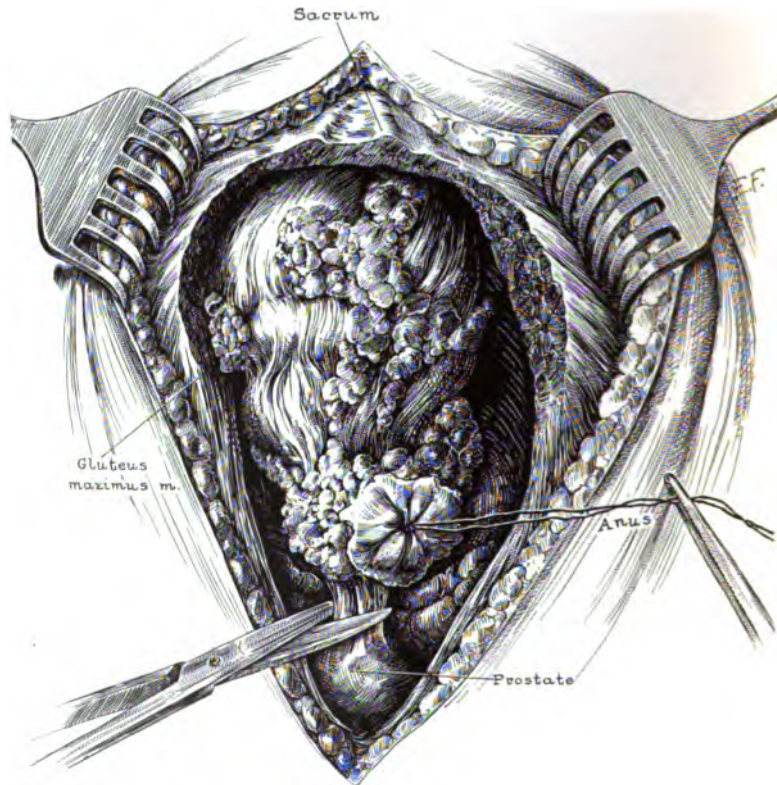
Fig. 182.—Kraske perineal excision of anus, rectum, coccyx, and lower sacrum.

attached to each other within the abdomen to prevent the engagement of small intestine, the doubled intestine is sutured to the parietal peritoneum at the point of emergence and the tumor packed roundabout with vaselin gauze. At the end of a few days the diseased area is excised with the cautery, both ends of bowel being left open, the upper acting as a temporary colostomy. From the second to the fourth day it is sometimes necessary, before amputation of the tumor, to puncture

the proximal side of the loop with a cautery, to deliver the gases.   In some instances the amputation of the growth may be primary, the ends of the bowel being held by crushing clamps for a few days.   From eight to ten days following the primary operation long-bladed crushing forceps are applied by passing one blade into each of the intestinal tubes, the tissues being crushed by tightening the forceps each day.   Usually
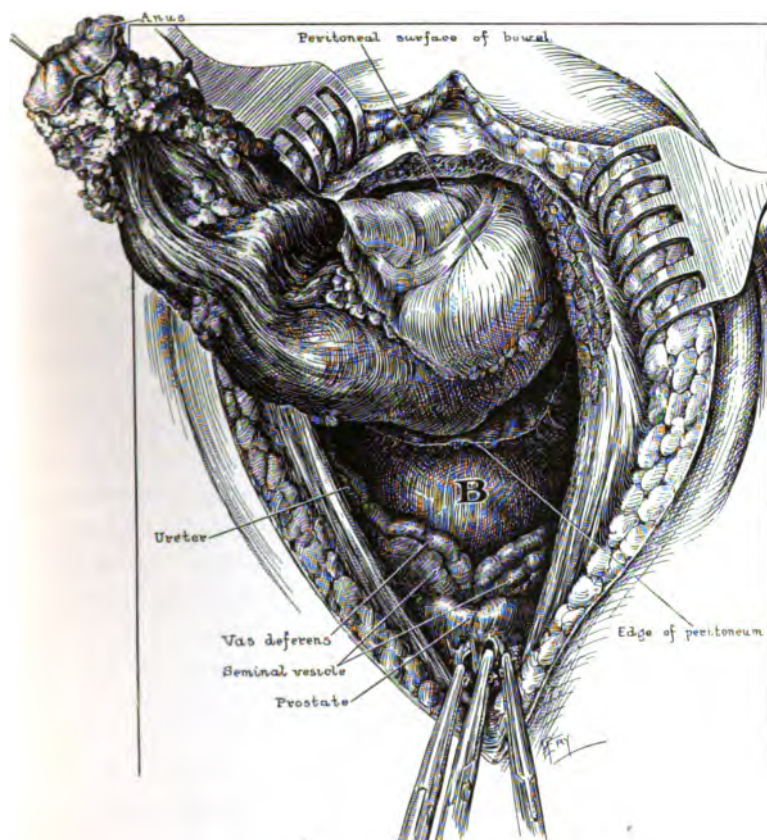
Fig. 185.—Removal of rectum and glands *en bloc* with pelvic peritoneum opened.

on the fifth day they cut through, making an entero-enterostomy from within the intestine.   In from one to several weeks later, according to the case, the external fistula may be closed.

This three-stage operation is one of the safest for the amount of diseased tissue removed.   It overcomes the dangers of leakage from resection.   In selected cases Bloodgood has obtained the same result in a

primary operation by resecting the growth, closing both ends, and connecting the sides of the sigmoid loop with a lateral suture anastomosis, the closed ends of the bowel being brought into the abdominal incision to be opened if necessary. We have accomplished the same thing by excising the tumor, uniting the proximal end of bowel to the sigmoid end-to-side, and bringing the distal end of the sigmoid into the abdominal incision, but not through the muscle. The end which is invaginated by a purse-string is not opened unless necessary for gas tension. A rectal tube is inserted for additional safety.

The combined perineal and abdominal one-stage operation is a very radical procedure and is responsible for a high mortality—20 to 36 per cent. Cripps has lowered this somewhat by making the abdominal pelvic dissection, closing the abdomen, and by posterior operation immediately elevating the rectum and sigmoid, the bowel not being cut off for two or three days.

RADICAL OPERATIONS FOR THE CURE OF CANCER OF THE SECOND HALF OF THE LARGE INTESTINE, NOT INCLUDING THE RECTUM*

WILLIAM J. MAYO

The early period of abdominal surgery was concerned chiefly with the question of mortality. With modern methods, it had to be definitely shown that, other things being equal, the opening of the abdominal cavity was comparatively safe. Under the able leadership of Tait in England, who might be called the father of modern abdominal surgery, and Price in America, the mortality was reduced to a point well under 5 per cent., and today standardized and accepted technic has reduced it to about 2 or 3 per cent.

However, the average mortality is somewhat on the increase, owing to the fact, first, that many operations in which there was practically little or no danger, and the results of which served to dilute, so to speak, the mortality of the more necessary operations, are no longer considered advisable, and, second, that modern methods have made possible a successful attack on conditions which were previously considered inoperable and which contributed to the higher death rate.

From the early period, in which everything was to be proved by the lowness of the mortality, we learned certain facts, among them, that even by the most careful methods of preoperative examination there is a percentage of error in accurate pathologic diagnosis not far from 10 per cent. This taught us that, except in the presence of acute infections or other contraindications, a careful exploration of the abdominal cavity is necessary before operating. It is to be regretted that an accurate pathologic diagnosis cannot always be made; but if we succeed in making a surgical diagnosis and cure the patient, we have, at least, accom-

plished the main purpose of the operation. It is immaterial to the patient, provided he gets relief, whether that relief comes through the removal of the appendix, gall-stones, or an ulcer of the stomach. Moreover, since a diagnosis brought up to the minute by exploration may reveal more than one lesion that can be relieved by a single operation, such exploration should be made unless there are definite contraindications. The patient who has had his appendix removed without an exploration and has been left with a duodenal ulcer or gall-stones, the real cause of his symptoms, to be taken care of at a second operation after months of suffering, has justifiable cause for dissatisfaction.

This brings up another important consideration—the disability resulting from the operation itself, which must be reduced to a minimum. If there is more than one pathologic condition which only operation will relieve, the disability will be greatly reduced if the two operations can be done in one stage. If the operations are performed at different times, the multiple risk may be as great at least as that of a single operation. While mortality statistics are reduced one-half when the number of operations is doubled, such an apparent reduction, obtained by doubling the number of operations performed on each patient, is misleading, and results only in prolonged disability. The two-stage operation, however, has great merit in a small group of cases in which the desperate condition of the patient justifies any maneuvers that will reduce the operative risk, and in which the question of disability becomes a secondary consideration.

In malignant disease, still another problem which is worthy of our most earnest attention and is naturally associated with the question of mortality is operability. Operability today is perhaps the most important consideration in connection with malignant disease. Low operability gives low mortality and high percentage of cures. An examination of the records of resections for malignant disease of the large intestine in our clinic definitely shows that when the disease was confined to the intestine and was movable, the mortality was well under 5 per cent., and the percentage of five-year cures above 60 per cent. Taken by itself, this certainly was a remarkable showing. When the operability was brought up to 62 per cent., the mortality trebled and the percentage of permanent cures markedly decreased, a most unfortunate showing; but when studied in the light of the entire group of cases, we had the paradox that more than twice the number of patients in each hundred were actually cured. This illustrates the fallibility of the view

that operative mortality percentages prove correct any theories based on such statistics, and leads others to the trite remark that "Nothing lies like statistics." Statistical percentages of mortality and cure can be studied properly only in their relation to operability. In other words, the greater the number of patients operated on to the hundred examined, the greater the mortality, because it brings in a group of advanced cases in which the risk of operation is great and the percentage of cures small. On the other hand, it increases by a definite and incontrovertible percentage the number of persons who have actually been cured.

From January 1, 1898, to December 31, 1915, 419 resections of the large intestine have been made in our clinic, with an average mortality of 14.5 per cent. In 184 of these cases the left half of the colon, including the splenic flexure and not including the rectum, was resected, with an average mortality of 17+ per cent. In resections of the right half of the colon the mortality was 12.5 per cent. The difference of 5.5 per cent. between the two mortality percentages was due to the less septic character of the liquid contents of the right half of the colon as compared with the more solid contents of the left half of the colon, and the greater safety of ileocolostomy as compared with the methods of union following resections of the left colon. One hundred and thirty-one of the resections of the left half of the colon were for malignant disease. Of each 100 patients presenting themselves, 62 were subjected to resection. In the remaining 38 the disease was considered inoperable at the time of examination, or proved to be inoperable on abdominal exploration. It is our earnest purpose to increase the operability, first, by endeavoring to secure the cases at an earlier date, and, second, by extending the limits of operability. Increasing experience shows that some of the cases, which at the time of examination we had considered inoperable, may be resected by modern methods with a prospect of permanent cure. In spite of the fact that this extension will add to the list many advanced cases, we should be able notably to reduce the death rate in the whole number by improvements in technic, and at the same time make the operation more radical.

Technical Considerations

1. An ample working incision should be made in the middle of the left rectus muscle. It is best to ligate the deep epigastric vessel above and below, and to excise the intervening section.

2. A thorough exploration of the involved colon and abdominal

cavity, especially of the liver and peritoneal tissues, should be made in order to discover possible metastasis or the direct involvement of other organs which would make a cure impossible.

3. *Mobilization.*—The most important consideration in resecting the large intestine is the detachment of the outer and posterior attachments of the colon so that it may be brought well out of the wound. If we remember that the large intestine has its origin on the left side of the body close to the midline and that it reaches its location around the outer circumference of the abdominal cavity comparatively late, we can readily understand that its outer attachments are in the general nature of holding bands and that they contain no structures of great importance. The splenic flexure is retained in position by the splenocolic ligament, which is derived from the omentum and contains a blood-vessel which must be tied. The outer leaf of the mesentery of the pelvic colon in the female is closely associated with the left broad ligament, and here again are vessels which must be ligated.

Posteriorly, the left ureter must always be identified and separated. As a rule, in the operable cases it is possible to detach the ureter safely from the growth; but in several instances we have found it necessary to resect a portion of it, tying the ends with catgut, when it was involved in a situation in which it was impossible to reimplant it in the bladder or suture the ends together. This permanent ureteral obstruction has not been followed by any unfavorable results, and in no case has it been necessary to remove the kidney at a later date because of it. On one occasion close attachments to the left kidney in an otherwise operable case made it necessary to remove the kidney with the growth. The patient has now remained well more than three years. The right ureter should be identified, but will seldom be found involved.

Attachments to the abdominal wall from direct extension of the growth are not infrequent, and we have not hesitated to remove large sections of the involved tissues when necessary. These extensive dissections did not add greatly to the mortality of the operation, and in some of the cases in which the growth was so fixed as to be apparently inoperable a cure has been effected.

It has been found wise, therefore, to loosen the colon from its outer attachments and remove all the involved tissues with it in a single piece. Among the most difficult dissections of this kind are those in which a previous exploration has been made, followed by a fecal fistula, or in which a colostomy has been performed for the relief of the obstruction.

Even in these complicated cases, however, all the structures of the abdominal wall on the outer side can be freely dissected if necessary, turning the colon and involved tissue toward the midline. The bleeding vessels are caught and tied, and a large gauze pack placed in the cavity, which is left undisturbed until the operation is completed, to check oozing from the cut surfaces.

When the colon containing the growth is drawn well out of the abdomen, it can be lifted up to the light and the blood-vessels readily identified and tied. The lymphatic supply of this region is scanty, and herein lies the success of these operations. In 60 per cent. of the fatal cases, according to Butlin, the patients die from obstruction, local infection, etc., before the glands are involved with cancer. Frequently, after extensive dissections, we have examined enlarged glands microscopically, and have found that the adenopathy was the result of sepsis and not of carcinoma. In a number of instances I have resected the colon in patients who had been previously explored and who had been refused radical operation on account of glandular involvement supposed to be carcinomatous. On removal, no cancer was found in the glands.

Segregation of the Involved Organs.—Having briefly outlined the character of the task of mobilizing the colon from the outer side, we must take into account the fact that the small intestine frequently becomes adherent to the carcinomatous mass on the inner side and there is direct extension of the disease. As a rule, the extension is to the periphery of the small intestine, although at times it involves the lateral wall of the mesentery. This complication, which we have seen often, by no means renders the condition inoperable, as is so frequently thought. We have several patients who have remained well beyond the five-year limit, in whom from one to three separated loops of small intestine had been resected with end-to-end union, and finally the diseased portion of the colon removed with the attached loops of small intestine. Experience with such resections of the small intestine has demonstrated the fact that almost any reasonable method of anastomosis will be effective— lateral or end-to-end. The general tendency is to take up too much time with these resections and suture more than is either necessary or desirable. Of late we have been more inclined to the end-to-end union with a continuous through-and-through chromic catgut suture, protected by a few interrupted silk sutures in the musculoperitoneal coats.

The ends of the small intestine which are left attached to the colonic tumor are crushed, ligated, and sterilized thoroughly with the cautery

to prevent soiling. In low sigmoid tumors the bladder is not infrequently involved, and on a number of occasions we have removed a considerable portion of its posterior wall. As a rule, only the peritoneal and muscular walls of the bladder are involved, and the mucous membrane is left intact. By the use of chromic catgut sutures protected by a few interrupted sutures of the same character, union seems to be very certain. I have never known a bladder so treated to leak following the operation.

Involvement of the ovaries and tubes and uterus is of small consequence. We have usually made an incision through the peritoneum in front of the cervix, cut the cervix directly across, grasping the uterine vessels and dissecting the broad ligament from below upward on each side, and removed with the uterus, the ovaries, and tubes, so that the whole mass remained attached to the sigmoid tumor. This is a safe procedure and leaves the adherent uterus to block the point in the bowel weakened by penetration of the tumor, which might otherwise be opened up and flood the operative field with septic contents. The ovaries should always be removed if any involvement is suspected, as they are the most frequent seat of cancer grafting of any organs in the abdominal cavity, probably because each ovulation opens up an unprotected surface for cell-grafting.

The appendix is rather frequently adherent to the tumor mass when the cancer lies low, and occasionally the cecum is attached. Removal of the appendix and the necessary amount of the cecum can be rapidly accomplished and does not seem to add greatly to the risk.

Excision of the Involved Colon and Restoration of Colonic Function.— In the manner briefly outlined, the colon and all the involved tissue are delivered outside the abdominal cavity. The further management will depend on how thoroughly we have been able to prepare the patients and whether or not there is obstruction. It has been shown that from one-fourth to one-third of the stool bulk is due to bacterial growth and that dry stool contains dormant bacteria, while liquid stools have most active organisms. It is undesirable that any attempt be made to evacuate the bowels by means of physic within twenty-four hours before the operation. This should be done at least forty-eight hours before, as liquid contents are difficult to control mechanically, as well as markedly infectious.

Primary resection in the presence of even moderate obstruction is seldom permissible. It is necessary in these cases, first, to relieve the obstruction, as a soggy intestine, edematous and septic, is extremely

liable to suture perforation.   We must content ourselves either with
a cecostomy under local anesthesia, which is best if the obstruction is
urgent, a colostomy made as close as possible to the growth so that it
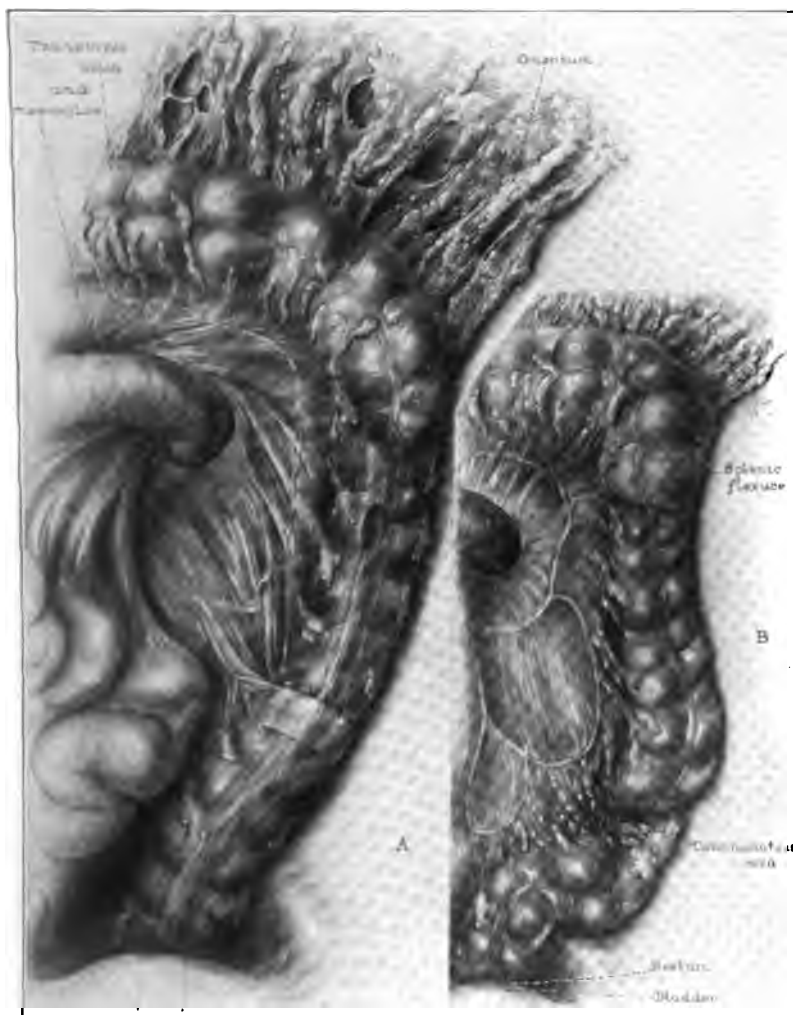
Fig. 184.—A. End-to-end tube resection completed; B, carcinoma of the pelvic sigmoid.   Dotted line indicates the points of resection.

can be excised when the resection is performed later, or, still better in the
large majority of instances, the two-stage operation of Mikulicz and
Bruns (Figs. 184 and 185).

'16—22

Many patients will come with obstruction of the bowels and in extremely poor condition for operation. At times, by lavage of the stomach and maintaining the fluids of the body if necessary by subcutaneous salines, such patients can be carried over the acute attack and subjected to operation later after flatus and bowel movement have been secured.

When conditions are favorable for a primary resection with an end-
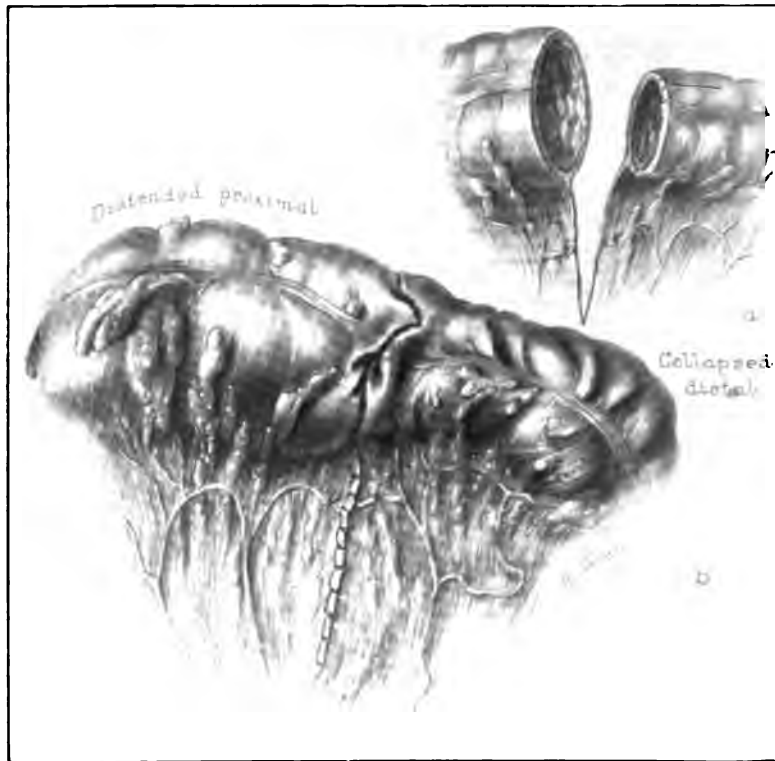
Fig. 185.—a, C. H. Mayo method of widening the distal collapsed bowel to meet the distended proximal bowel; b, operation completed.

to-end anastomosis, the use of the sigmoid tube (Fig. 184), that is, a rubber tube of considerable caliber, which, as advised by Balfour, is passed from the anus completely through the anastomosed area and some inches above, will reduce the death rate to a very great extent. We frequently pass these tubes well up into the splenic flexure. A large-sized, rather firm stomach-tube with a few lateral eyes near the tip will answer the purpose.

The sutured area should be attached to the peritoneum if there is any doubt whatever as to the integrity of the suture line, or it may be brought completely through the peritoneum, the latter being attached behind it so that it lies within full view, and any leakage will be to the surface.   If the colon is too short for this maneuver, the sutured area
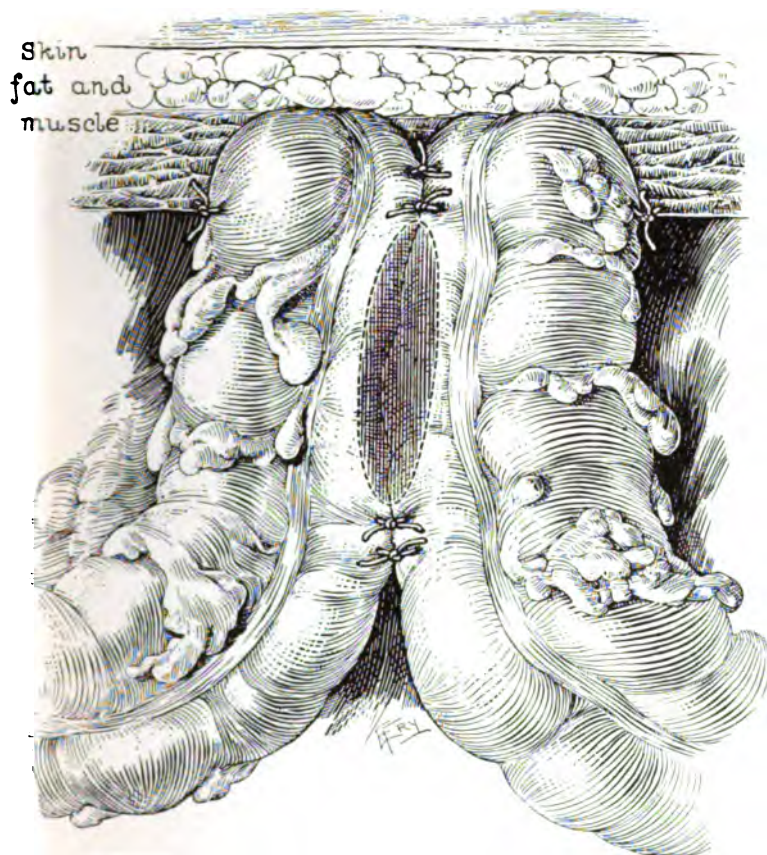
Fig. 186.—Bloodgood method of anastomosis of the large intestine. The bowel is attached to the incision in such a way that, should leakage occur, it would readily find its way to the surface.

may be suspended on a roll of rubber tissue so that it will develop adhesions and the suture line will become extraperitoneal.

In applying the end-to-end suture there is an unconscious tendency to draw the sutures tight, so as to narrow the lumen.   This can be easily overcome, as suggested by C. H. Mayo (Fig. 185), by making an incision along the free surface of the colon opposite the mesenteric attach-
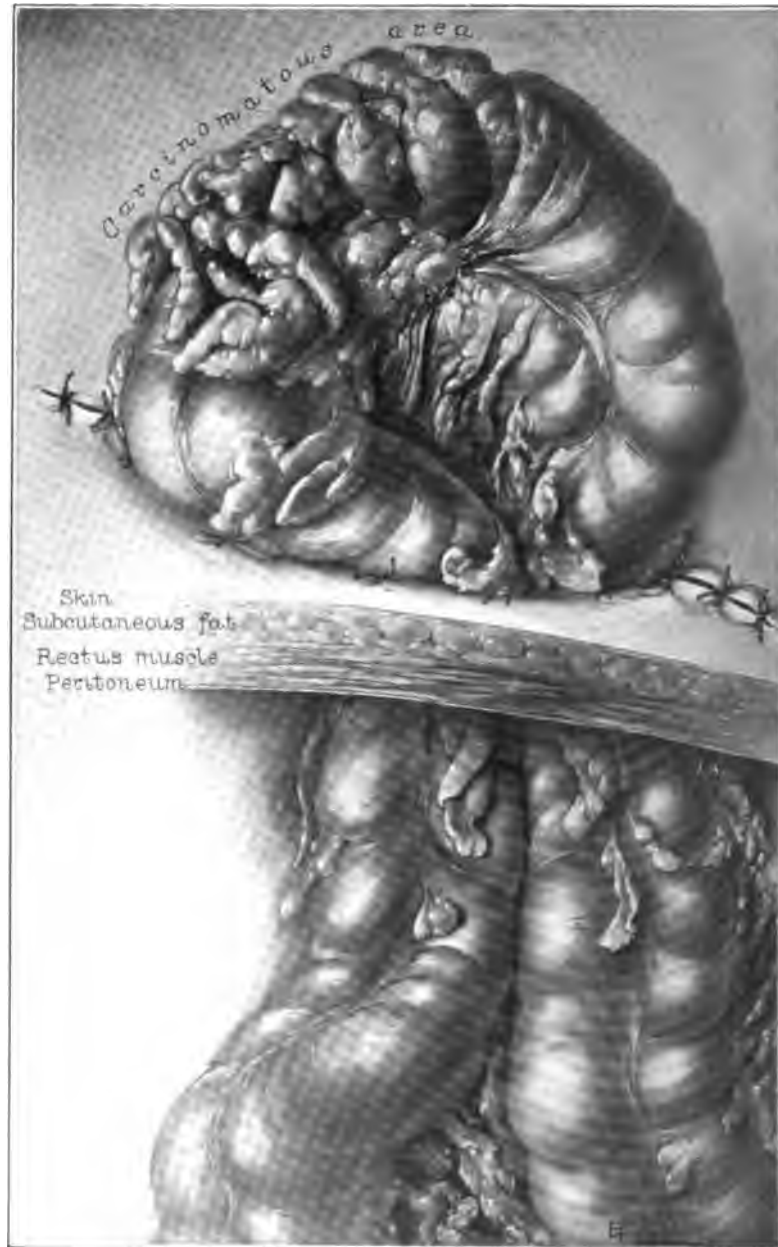
Fig. 187.—First stage of Mikulicz operation completed. The tumor, involving part of bowel, fat, and mesentery being drawn outside the abdominal wall, where it will remain until it heals in. It will then be cut away, and the partition between the limbs of the bowel, as sutured together, will be cut out with forceps, the lumen being restored and the colostomy closed.

ments three-fourths of an inch deep on each side, and trimming off the corners.   When the suture is complete, the lumen is widened to that extent at the point of anastomosis.   The Bloodgood method of colonic anastomosis also serves an excellent purpose.   A drawing of this method is here shown, and is so plain that it needs no further description (Fig. 186).   The tube method of end-to-end anastomosis described by Balfour is especially valuable following resections of low sigmoid growths.

About twelve years ago C. H. Mayo introduced into our Clinic the Mikulicz-Bruns method (Fig. 187) of resecting the second half of the colon, and this method has probably done more to extend operability and reduce mortality than any other factor.   It consists in loosening up the diseased portion of the colon, as already described, separating the mesentery, and lifting the growth and glands with the involved tissues entirely out of the abdomen.   The sound colon for several inches above and below is well cleared and the two arms sutured, the tumor and a sufficient quantity of intestine being left completely outside the abdominal cavity.   The peritoneum is sutured around the base of the extruded mass so that it becomes entirely extraperitoneal, and is allowed to heal into the incision.   In from three to seven days the mass is cut off, the two ends of the intestine being left like a double-barreled shotgun in the wound.   If there is obstruction, the method of Paul is advisable; that is, after the sigmoid is fixed firmly in the wound to prevent retraction within the abdomen during sudden strain (coughing, etc.) the tumor mass is cut away, leaving the ends of the sigmoid projecting an inch or more.   A rubber tube, 1 inch in diameter, is fastened into the proximal bowel end to carry the obstructed contents into a container. In many cases in which the circulation in the extruded loop is cut off it is good practice to cut the tumor away at once after tying and sterilizing the ends of the bowel, as advised by Peck.   This prevents soiling for from twenty-four to forty-eight hours until the wound is protected, and if the patient has been well prepared the temporary obstruction is borne without difficulty.

At a second stage, about ten or twelve days after the primary operation, during which time the bowels have been thoroughly evacuated, one blade of a four-inch clamp is placed in each opening of the colon and the clamp closed to the first notch.   Each day it is tightened until, at the end of about six days, it has cut its way through, converting the outer end of the double lumen of the intestine into a single cavity.   A few days later the resulting colostomy can be closed by a simple extraperitoneal

operation. It might be thought that with better technic a larger percentage of these cases could be subjected to immediate resection, but it is not technical faults in suturing that lead to disaster. If leakage occurs, it is usually in the second week, owing to perforations in the suture line after the sutures have fulfilled their mission. We have found chromic catgut for gastro-intestinal suture less liable to this complication than silk or linen.

The operation of Mikulicz can be applied to very low growths. It is astonishing to what extent even the upper part of the rectum can be brought into the abdominal wound. On many occasions we have removed rectosigmoid growths in this way, separating the rectum within an inch of the anus, and by loosening and depressing the parietal peritoneum, have succeeded in maintaining the growth exterior to the abdominal cavity. Often it is necessary to pack gauze about the protruding mass to support it in the wound beyond the peritoneum. The gauze support should be left from ten to sixteen days. In very fleshy patients in whom it has been practically impossible to bring the growth to the surface we have in this manner brought the involved bowel up just outside the peritoneal cavity, and left it in the deep wound with an iodoform gauze support as long as eighteen days. When the tumor is finally cut away, the anastomosis will often complete itself without any secondary operation.

Occasionally, abscess cavities of considerable size will be found in the pelvis. These by no means necessarily indicate that the growth is inoperable, but they require the complete closure of the pelvis following the operation by loosening up and attaching the peritoneum so as to protect the abdominal cavity, and in the female by draining through the vagina. In the male the entire small pelvis must be packed with iodoform gauze. These abscesses are more often found in the female than in the male, possibly because of the proximity of the fallopian tubes.

At times it is better to terminate these extensive complicated operations for rectosigmoid cancer by a permanent colostomy above, applying a right-angled clamp across the rectum below the growth and sterilizing the stump with the actual cautery. The necessary amount of involved sigmoid is then cut away and the proximal end brought out of the median incision just below the umbilicus as a permanent colostomy, after the method of Mixter. The cavity of the pelvis about the clamps is packed with iodoform gauze. The clamps are removed at the end of

a week, and the gauze the latter part of the second week. As a rule, it will be best to fasten the peritoneum at the brim of the pelvis to the sigmoid.

To one who has not actually taken part in some of these formidable operations they might appear impossible, or even if mechanically possible, to be fraught with so much immediate danger and so little chance of permanent cure as not to be justifiable. This is by no means true, however, for after such extensive and complicated dissections we have had a very considerable percentage of permanent cures, and in the cases in which the disease has returned the patient has had a long respite of comfortable existence which could not have been obtained by a palliative colostomy.

There were 262 resections of the large intestine for malignancy. Of the patients who recovered and who were operated on more than five years ago, 54 per cent. are alive. Of those operated on more than three years ago, 67.5 per cent. are alive.

In conclusion, I would urge that patients with cancer of the second half of the colon be given a chance even under unfavorable conditions, because the nature of the disease is such that the prospects of cure are better than for cancer in any other situation in the body, except on the lip and in the fundus of the uterus.

THE RADICAL OPERATION FOR CANCER OF THE RECTUM AND RECTOSIGMOID*

WILLIAM J. MAYO

It is my purpose in this communication to discuss briefly five problems connected with cancer of the rectum and rectosigmoid: First, operability; second, operative mortality; third, operative disability; fourth, function following operation; and fifth, permanent cure. The discussion is based on a study of 753 patients whose histories were recorded in our clinic between January 1, 1893, and December 31, 1915. Of these, 430 were subjected to radical operation.

Operability.—From January 1, 1910, to December 31, 1915, 619 patients with cancer of the rectum and rectosigmoid presented themselves for examination. A radical operation was performed on 312. In 186 the disease was so far advanced that operation was not advised; in 32 operation, though advised, for various reasons was not performed; in 89 on abdominal exploration the condition was found inoperable and the operation was terminated either as an exploration or as a palliative colostomy. Eliminating the 32 cases in which operation was advised but not performed, we have 275 belonging to the group in which a radical operation was not thought possible, against 312 in which radical operation was performed—an operability of 53.1 per cent. It is interesting to note in this connection that Harrison Cripps found it advisable to perform the radical operation on only 107 of 445 patients, an operability of less than 25 per cent.

In the three years just passed—1913, 1914, and 1915—277 patients with cancer of the rectum and rectosigmoid were examined and 199 were subjected to radical operation, an operability of 71.8 per cent., the increase being due to the fact that we did not refuse radical operation because of the local extent of the disease unless it involved structures which made its eradication impossible. In 6 cases a total hysterectomy

was performed coincidentally because of extension of the disease to the uterus. The posterior wall of the vagina was removed in 12 cases. In 6 a part of the posterior wall of the bladder was resected. The whole or a part of the prostate and one or both seminal vesicles were removed in 11. In 2 instances the pelvic portion of one ureter being involved, the diseased portion was resected and the ends of the cut ureter were tied with catgut, without causing marked symptoms from complete obstruction of the ureter. In another patient the greater part of the membranous urethra, the prostate, both seminal vesicles, and the posterior half of the neck of the bladder were involved; these were removed. The patient lived nearly three years in good health before dying of metastasis. In 5 cases one or more loops of small intestine were resected because of direct extension from rectosigmoid cancer.

Ill-advised operations added very largely to the mortality, and in many instances, had it been possible to know the extent of the disease in advance, we would not have operated. It is a fact, however, that many patients with advanced disease not only recovered from the operation but remained well, and those who survived the operation and died later of recurrence received greater palliation and longer lease of life than would have followed colostomy.

Cancer of the rectum is not prone to early lymphatic involvement, tending to remain a localized process until late. In no case was lymphatic extension alone the cause of inoperability. Some patients in whom the rectal glands were involved have recovered and remained well following the radical operation, but none of our patients in whom the inguinal glands were involved made a permanent recovery, even after the most extensive glandular excision. The most frequent cause of inoperability was local extension of the disease to neighboring organs; the next in frequency was metastasis in the liver; and the third, peritoneal and retroperitoneal metastases.

Theoretically, at least, the abdominal cavity should be explored in every case of carcinoma of the rectum because of the frequency with which metastases in the liver or peritoneal cavity are to be found, and unless such an exploration be made before a radical operation is undertaken, a number of patients will be subjected to a serious and mutilating operation without the possibility of cure.

Cancers which involve the upper rectum cannot be separated surgically from cancers of the terminal sigmoid. There seems to be a marked tendency for high cancer of the rectum to invade the sigmoid

and those in the sigmoid to extend into the rectum proper. Hence it may be impossible to determine whether a given growth was primary in the terminal sigmoid or in the upper rectum. It seemed wise, therefore, to classify high rectal and terminal sigmoid cancers in one group as rectosigmoid cancers. In this group the question of operability is most difficult to decide.

Operative Mortality.—The mortality of the operation itself depends, to a large extent, on what cases are accepted for radical operation and how radical an operation is performed. For example, we performed 30 radical operations by the Harrison Cripps method without a death. but the number of cases in which this operation may be applied is limited if the patients' best interests are considered. Cases which, in our early experience, we would not have considered operable, we now subject to operation for reasons already given. Again, an operation considered sufficient in the first period was not considered sufficiently radical at the later period. Of the 753 cases, a radical operation was performed in 430, with an operative mortality of 15.5 per cent. During the period from 1893 to 1910 the operative mortality was 17.8 per cent.; from 1910 to 1913 it was 17.7 per cent., with an operability of 51 per cent.

For the years 1913, 1914, and 1915 the mortality averaged 12.5 per cent., and the operability 71.8 per cent., while the operations were made more radical. Increased experience has now brought this mortality to about 10 per cent., and a wiser selection of cases for operation will still further reduce the death-rate.

Comparison of the mortality in cancer of the rectum in various clinics shows that low mortality is coincident with low operability. An operability of 25 per cent. in our Clinic would have reduced the mortality to a point under 5 per cent., since it would have eliminated cases with advanced disease which give the high mortality. It is a question of an advancing frontier in which large operability gives an apparently high mortality and a low percentage of cures, with the paradox that when the total number of cases is taken into consideration it will be found that a larger number of patients have been cured. In other words, operative mortality means nothing unless the total number of cases examined is taken into consideration.

All patients dying in the hospital after the radical operation were classified, without regard to the length of time that elapsed before death occurred, as having died from operation. Many of these patients died after some weeks from nephritis, cardiovascular disease, etc., which

they had at the time of the operation.   However, there seems to be no
way of properly estimating mortality without including them, and a
certain amount of statistical hardship must be accepted in order that we
may have a common basis for computation.   Consent is obtained for
necropsies on about 95 per cent. of the patients who die in the Clinic.
When an operation has been performed, we make it a rule that the
operating surgeon or one of the surgical assistants shall attend the
necropsy in order that his exact technical knowledge of the operative
procedure may aid the pathologist in arriving at the primary and con-
tributory causes of death.

Among the facts which were especially apt to increase the mortality
was obesity, the fat patient, especially the male, giving almost a pro-
hibitive mortality from the one-stage combined abdominoposterior
operation.   However, obese patients withstood well the two-stage opera-
tion and also operations of the perineal or posterior Kraske type, though
in the case of very obese persons the colostomy itself was sometimes
made with difficulty and was attended by a very considerable risk.   In
such patients we have not infrequently made the posterior radical opera-
tion in a single stage, without exploration or colostomy, completing the
operation with a posterior anus at or near the normal situation.

The important causes of operative mortality are:

1. Sepsis, 39.8 per cent.   The sepsis was due usually to soiling the
wound or peritoneal cavity with intestinal contents during the operation.
This occurred most frequently in cases in which the growths had caused
obstruction;   consequently, radical operations are seldom permissible
until the obstruction has been relieved.   In cases of this kind the two-
stage operation proved of the greatest value.   The colostomy relieved
the obstruction and made possible thorough cleansing of the lower frag-
ment, which, by reducing the infection, tended to produce more favorable
conditions for operation later.   The disadvantage of this method lay in
the fact that the blind stump created between the colostomy and the
point where the lower sigmoid was turned in behind had a tendency to
develop late infections, fistulas, etc., in the posterior wound.   It would
appear that the percentage of deaths from sepsis was too high and un-
doubtedly this is true.   Few of the patients in whom the growth was
movable died from sepsis following operation, but we found it exceedingly
difficult to prevent soiling of the wound in those cases in which the
rectum was fixed and the growth had completely penetrated through the
walls of the rectum, especially when this fixation took place in a situation
where the peritoneal cavity was involved.   This was particularly true

of the rectosigmoid cases in which the operation was necessarily per-
formed from above—cases often complicated with abscesses in the pelvis
and adhesions to the small intestines. In this group the mortality was
more than 30 per cent. One might well ask: Is it justifiable to attempt
the radical operation under these circumstances? The answer depends
upon the point of view. Colostomy in such cases is a most meager
palliation and the fact remains that in nearly 20 per cent. of such ex-
tremely advanced cases in which the radical operation was performed,
a five-year cure was obtained.

2. Nephritis, 13 per cent.; usually an acute nephritis superimposed
on a chronic process. Infections, hemorrhage, and interference with
the function of the bladder played a considerable part in its production.
The post-operative subcutaneous introduction of fluids into the general
circulation is most important in preventing this complication.

3. Undiscovered metastatic tumors, 10.5 per cent. Unfortunately,
abdominal exploration does not always reveal such growths, especially
when they are buried in the substance of the liver, by all odds the most
common condition. Small areas of cancerous involvement in the
peritoneum and posterior fatty tissue are also sometimes overlooked.
Patients with metastatic cancer have little vitality and often die from
exhaustion following an operation which would not have been performed
had the true condition been known. By more thorough exploration
some of these operations and deaths have been avoided, though not all.

4. Hemorrhage, 6.5 per cent. While no patient died from hemor-
rhage directly, two died from so-called secondary shock, due to loss of
blood from poorly controlled hemorrhage. In the remaining cases in
this group hemorrhage was the chief factor leading to infection and ex-
haustion. We have not found that extensive operations of themselves
have added very greatly to the mortality unless accompanied by in-
creased loss of blood. In other words, unless there has been hemor-
rhage, I have not seen shock, the patients being in excellent condition
at the completion of the most formidable procedures. Prolonged opera-
tions with great traumatism may cause shock without actual loss of
blood, but the condition is the same, the blood being withdrawn from
the general circulation and lying in the suddenly dilated venous trunks
of the abdomen.

5. Obstruction of bowels following operation, 3 per cent. In clos-
ing the gap in the pelvic peritoneum to prevent the entrance of the
small intestines into the space from which the growth has been re-
moved a continuous chromic catgut suture should be used. I lost two

patients some time after operation from chronic obstruction of the bowels, because I had used interrupted chromic catgut sutures, and following the operation part of the lateral wall of the small intestine had pushed through a little crevice in the suture line.

In one case death was due to the inclusion of both ureters in suturing the peritoneum to close the pelvic cavity. The ureters had been in full view, but too much of the peritoneum and lateral structures of the pelvis were taken up in the suture in the attempt to secure a firm closure.

The remaining deaths were due to exhaustion and occurred usually some days or weeks after operation.

Operative Disability.—Asepsis leads to primary wound healing. We have had patients leave the hospital with completely healed wounds in sixteen days and return to their employment in thirty days. Infected wounds were often six to twelve weeks in healing, and three or four months occasionally elapsed before the patients returned to work.

Function Following Operation.—The best function that we have been able to obtain following operation has been after the tube method of resection described by Balfour and the C. H. Mayo method of direct end-to-end union between the end of the sigmoid and the anal canal. The Weir method of invaginating the growth through the anus—amputation and direct through-and-through suture from the mucous surface—has given excellent results, but can be practised in only a small number of cases. The attempt to save function, however, has been one of the most common causes of technical failures, resulting in sepsis and death or failure to obtain permanent cure. In order to save function, modifications resulting in a less thorough eradication of the disease were made in the operative technic. Patients, as a rule, were willing to accept a definite increase in possible mortality and a reduction of prospects of permanent cure that the function so highly desirable might be obtained.

The manner of performing colostomy does not seem to have made much difference in the ultimate functional results, but in any event the opening should be made well above the pudendal hair, which, when soiled, tends to uncleanliness and fecal odor. We have had good results with the Littlewood method, which places the colostomy in the waist line above the left anterior superior spine of the ilium. This obliterates the peritoneal space to the left of the colostomy and prevents the incarceration of the small intestine and its adherence in this situation. In two cases in our experience colostomy in the left rectus muscle was followed by obstruction of the bowels from this cause.

Mixter advises making the colostomy in the midline just beneath the umbilicus, and we have used this situation in a number of instances with satisfaction. The Mixter colostomy furnishes direct access to the lower sigmoid and rectum and facilitates cleansing, when made as the first stage of a two-stage operation. It also appears to be less liable to late infections in the blind end following the radical operation. Moreover, it rapidly terminates a midline exploration or radical operation by placing the colostomy in the upper end of the working incision, and the results are so satisfactory that we are employing it extensively.

Care in regard to diet, the development of a forty-eight-hour habit of bowel movement and the use of a large amount of water as an enema to empty the large bowel thoroughly once in twenty-four to forty-eight hours, does much to render the management of a colostomy successful. The radical operation of Harrison Cripps, while applicable only to cancer of the low rectum and anal canal, gives marvelously good functional results. In those cases in which extensive dissections about the bladder, prostate, urethra, etc., have been made, the return of control of the bladder is sometimes slow. One of our patients lost control of the bladder to a large extent permanently, and catheter life is necessary. This patient is impotent.

Permanent Cures.—Of the 430 patients on whom a resection was done, 364 recovered from the operation. Eliminating those who were operated on less than three years ago, we have 33.3 per cent. who lived three years or more, and 28.3 per cent. who lived five years or more, after the operation. These percentages may be increased fairly to 37.5 and 35.8 per cent., respectively, by subtracting from our mortality figures the normal death-rates for corresponding ages for periods of three and five years, *i. e.*, 4.2 and 7.5 per cent.*

REFERENCES

Balfour, D. C.: "A Method of Anastomosis Between Sigmoid and Rectum," Ann. Surg.. 1910, li, 239–241.

Cripps, H.: "On Diseases of the Rectum and Anus," London, Churchill, 1913, pp. 449–515.

Littlewood, H.: "Malignant Disease of the Colon: Fourteen Colectomies with Ten Recoveries," Lancet, 1903, i, 1511–1515.

Mayo, C. H.: "Resection of the Rectum for Cancer with Preservation of the Sphincter," Surg., Gynec. and Obst., 1914, xviii, 401–403.

Mixter, S. J.: "Points in the Surgical Treatment of Acute Intestinal Obstruction," Surg., Gynec. and Obst., 1915, xx, 268–270.

Weir, R. F.: "An Improved Method of Treating High-Seated Cancers of the Rectum," Jour. Amer. Med. Assoc., 1901, xxxvii, 801–803.

* Medico-Actuarial Mortality Investigation Table.

UROGENITAL ORGANS

THE FATE OF PHENOLSULPHONEPHTHALEIN WHEN INJECTED INTO THE ANIMAL ORGAN- ISM. FACTORS OTHER THAN THE KIDNEY IN- FLUENCING ITS "RETENTION"*

(Preliminary Report)

EDWARD C. KENDALL

During the past few months I have been engaged in a study of the physiologic action of the thyroid. The general scheme followed has been to give a timed intravenous injection[1] of amino-acids, sugars, and other substances in conjunction with the injection of the active constituent of the thyroid, and to study the effect of the thyroid on the metabolism of the animals. Some animals respond very vigorously, the injection of the thyroid constituent producing very high pulse-rate and a great increase in the respiration, accompanied by an extremely severe general tetany and terminating in a temperature which occasion- ally reaches as high as 112° F. It was soon found that all animals can be divided into two classes—those that give this reaction and those that do not.

For certain reasons it seemed probable that the condition of the animal could be foretold by the use of some substance which would be a criterion prior to the injection of the thyroid hormone. Phenolsulphone- phthalein was used for such a test, and a few trials demonstrated that in those animals which had a high phthalein retention very little or no effect was produced by the injection of the thyroid and in those animals having a low phthalein retention a vigorous response to the thyroid might be expected. The administration of the phthalein was changed somewhat from the usual procedure, and 1 c.c. per hour of the standard solution (6 mgm.) was injected continuously during the entire experiment. By taking samples of the urine every fifteen or thirty minutes the exact

condition of the animal could be closely followed.   At first it seemed that
the type of metabolism going on had some influence on the amount of
phthalein excreted.   With a constant injection of glucose we have
recovered as high as 98 per cent. of the phthalein injected.   This very
high return was not momentary, but continued for several hours.   When
a dog was injected with amino-acids it was found that a rather low
phthalein output resulted, and in one instance a maximum excretion of
47 per cent. was found.   In a second animal the maximum was 52 per
cent.   As it seemed probable that the type of metabolism going on in
the animal was one factor controlling the output of phthalein, we were
greatly surprised to find that on the injection of amino-acids in a third
dog the phthalein output ranged from 80 to 86 per cent. for many hours.
It was necessary, therefore, to go further back for an explanation of the
phthalein retention.

In order to determine whether the phthalein was absorbed and held
in the tissues the dogs were killed and their organs examined for phenol-
sulphonephthalein.   In no case were we able to recover any of the
dye except slight traces in the blood.   Phthalein retention, therefore,
assumed a new aspect; that is, phthalein retention really means phthal-
ein destruction.

The possible mechanism of the destruction of phthalein may be,
first, the hydrolytic cleavage of the substance;   second, the oxidation
of the compound, and third, reduction.

The first is improbable because it is unlikely that there is a specific
enzyme in the body that will accomplish it.   On trying to oxidize
phenolsulphonephthalein with hydrogen dioxid it was found to be
extremely resistant.   A similar trial with nascent hydrogen showed that
it is easily reduced.   It thus seemed probable that phthalein in the
body is destroyed by reduction.   In order to establish this point a dog
was killed, its various organs ground to a fine mash, and 1 c.c. of phenol-
sulphonephthalein was mixed with the tissues.   After standing some
hours the amount of phthalein destroyed was determined.   It was
found that muscle and intestine destroyed a large percentage; that the
liver destroyed practically 100 per cent.;   and that the spleen, pancreas,
lung, and kidney destroyed almost none.

If the destruction of phthalein in the tissues is caused by its reduction,
the presence of an oxidizing atmosphere should prevent the destruction of
the dye.   To show this, a liver mash was mixed with phthalein, one por-
tion was covered with liquid petrolatum to exclude oxygen, a second was

left exposed to the air, and through a third portion air was bubbled. In the portion in which no oxygen was present the phthalein was totally destroyed; in the dish standing open, a large percentage but not all was destroyed; and in the portion through which air was bubbled only a portion of the phthalein was destroyed. Blood, both in the oxidized and in the reduced form, will not destroy phthalein. Its destruction in the tissues is caused by a more powerful reducing action than that of completely reduced hemoglobin. Since blood is the carrier of oxygen in the body, it seemed probable that there would be a difference in the destruction of phthalein by a perfused liver if the blood in the perfusing fluid was oxygenated or reduced. In the presence of oxygenated defibrinated blood as much as 80 per cent. may be recovered after perfusion of a liver. In contrast to this 95 per cent. of the phthalein perfused through a kidney was recovered, although reduced hemoglobin was used.

These experiments have been confirmed and enlarged with the object of showing the presence of an enzyme in the tissue which is capable of exerting a very strong reducing action. It is not probable, however, that this enzyme acts on the phenolsulphonephthalein itself. Phthalein is not affected by mild reducing agents, such as hydrogen sulphid, sulphurous acid, ammonium polysulphid, and formaldehyd, and apparently will not react except with nascent hydrogen itself. The presence of reducing enzymes in plant and animal tissues has long been known, and the fact that phenolsulphonephthalein is apparently reduced only by nascent hydrogen and is destroyed in the animal organism furnishes grounds for speculation concerning the possibility that hydrogen is produced by the tissues of the body. If hydrogen itself is not produced, there is at any rate a most powerful reducing substance. The reducing action appears to proceed according to the laws generally followed by enzymes; that is, it is destroyed by heat, its activity is greatly influenced by minute amounts of acid and alkali, and also by the presence of sugars and other materials. The fact I wish to emphasize is that this enzyme continues to exert reducing action both in the presence and in the absence of oxygen. Is it not probable that a primary step in metabolism is a reduction with the production of hydrogen, which then reacts with hemoglobin? If the supply of oxygen from hemoglobin is adequate for the reducing action of the cells, then phenolsulphonephthalein can no longer be reduced, as it is protected by an excess of oxygen. However, if the reducing action of the cells is greater than can be satisfied by the

oxygen from the hemoglobin, phenolsulphonephthalein is reduced. Fundamentally, therefore, what the phthalein tests show is the relation between the rate of reduction and the supply of oxygen in the body. Just what the phthalein indicates in any particular case obviously depends on so many factors that it is impossible to localize all the effects in any one organ.

The presence of a slight acidosis increases the capacity of the tissues for absorption, so that they will retain the dye so firmly that it cannot be washed out with physiologic salt. The addition of a small amount of sodium carbonate will counteract this, and physiologic salt will then remove the dye from the tissues. Furthermore, in the presence of an increase in the hydrogen ion concentration the action of the enzyme is apparently more vigorous, resulting in greater destruction of phthalein. Acidosis is not controlled by any one organ, but is a condition which may result from many causes. That it plays its part in the destruction of phthalein cannot be doubted. Another great factor is the rate of the circulation of the blood. If for any reason the blood passes through the tissues at a slightly diminished rate, the amount of oxygen supplied to the tissues is reduced, and the excess necessary to protect phthalein from destruction is no longer present; thus a greater destruction of the dye results. Another factor would be a condition of anemia, in which the oxygen-carrying capacity of the blood is greatly reduced. Finally, also, the lungs must play a very important part, as improper aëration of the blood would cause inability of the hemoglobin to furnish enough oxygen to protect the phthalein from destruction. We have produced a drop in phthalein output from 76 to 19 per cent. in an animal receiving a continuous injection of phthalein, by simply interfering with its respiration. When the respiration was again normal, the output rose to 60 per cent. If the kidney does not readily pass the dye, it is returned to the circulation and the tissues have a prolonged action on it, resulting in greater destruction.

There is one condition which I should like to mention in which this enzyme, with its ability to produce extremely powerful reducing substances, if not nascent hydrogen itself, may play an important part. It seems highly probable that in uremia, when there is a condition in which phenolsulphonephthalein is reduced, other substances must be reduced, not directly by enzyme action, but by the action of hydrogen or its substitute. Such reduction going on constantly within the tissues of the body is at least theoretically capable of producing compounds

which normally could not be present, and to these compounds originating within the organism itself we may attribute some of the clinical symptoms.

For the treatment of blood, tissues, and other body fluids so that a phthalein test may be made a method somewhat similar to one already described has been used.[23] The material to be tested is made to some definite volume and placed in a beaker. Ten to 15 c.c. of concentrated ammonia is added and 5 to 10 grams of calcium chlorid. The solution is then boiled. The calcium precipitates the proteins, and this precipitation, in the presence of ammonia, leaves the dye in solution. If there is a slight opalescence following this treatment, it has been found that the addition of ammonium phosphate, which will precipitate calcium phosphate, will remove the last traces of turbidity and leave a solution which can be accurately matched with the standard. The water is allowed to boil off until somewhat below the original volume. The solution and precipitate are returned to the original measuring vessel, cooled, made up to the original volume, and filtered.

In the following tests the same procedure was followed throughout: The finely ground tissue was mixed with 1 c.c. of standard phenolsulphonephthalein solution and allowed to stand undiluted or diluted with physiologic salt and other additions, as shown in the table. The solutions were preserved with toluol, and bacterial action can be ruled out as a possible factor of the destruction. Dilution appears greatly to influence the amount of phthalein reduced probably by simply diluting the concentration of the substance reducing the phthalein. Another factor which may be of influence here is the diminished activity of the diluted solution. The partial destruction of the enzyme by simply allowing the liver mash to stand in the laboratory until in a putrid condition is of interest. Although there is no doubt about the presence of bacteria in this case and although bubbles of gas were being given off by the solution, the destruction of phthalein was very much less than before the liver had become decayed. This loss of action when the tissue became decayed suggests that the reducing enzyme is more active in living, functioning cells and that the destruction of phthalein in these experiments and in the body is not caused by the degenerative processes going on in dead cells. Whether or not the favoring action of glucose on the destruction of phthalein is of significance is not now certain, but it is of interest to note that the solution causing the greatest destruction of phthalein contained small amounts of glucose.

Tissue	Amount Gm.	Phthalein c.c.	Treatment	Phthalein Recovered. Per Cent.	Remarks
Sheep's liver	50	1	Undiluted+liquid petrolatum	0	
" "	50	1	Undiluted. Exposed to air	Trace	
" "	50	1	150 c.c. 0.8 per cent. NaCl+liquid petro-latum	47	
" "	50	1	150 c.c. 0.8 per cent. NaCl. Exposed to air	78	
" "	50	1	150 c.c. 0.8 per cent. NaCl. Aërated	90	
Human liver	25	1	40 c.c. 0.8 per cent. NaCl	10	
" "	25	1	39.5 c.c. 0.8 per cent. NaCl+0.5 c.c. 3 per cent. H_2O_2	30	
" "	25	1	35 c.c. 0.8 per cent. NaCl+5 c.c. 3 per cent. H_2O_2	30	
" "	25	1	25 c.c. 0.8 per cent. NaCl+15 c.c. 3 per cent. H_2O_2	44	
" "	25	1	40 c.c. 0.8 per cent. NaCl+0.5 gm. glucose	9	
" "	25	1	40 c.c. 0.8 per cent. NaCl+5 gm. glucose	20	
" "	25	1	40 c.c. 0.8 per cent. NaCl+15 gm. glucose	33	
" "	25	1	39.5 c.c.0.8 per cent. NaCl+0.5c.c.$\frac{N}{10}$NaOH	11	
"	25	1	35 c.c. 0.8 per cent. NaCl+5 c.c. $\frac{N}{10}$NaOH	25	
" "	25	1	25 c.c. 0.8 per cent. NaCl+15 c.c.$\frac{N}{10}$NaOH	77	
" "	25	1	40 c.c. 0.8 per cent. NaCl+boiling	100	Enzyme entirely destroyed
" "	25	1	40 c.c 0.8 per cent. NaCl. Allowed to become putrid by standing four days	30 / 90	Enzyme partially destroyed
Human kidney	25	1	40 c.c. 0.8 per cent. NaCl		
" "	25	1	39.5 c.c. 0.8 per cent. NaCl+0.5 c.c. 3 per cent. H_2O_2	90	
" "	25	1	35 c.c. 0.8 per cent. NaCl+5 c.c. 3 per cent. H_2O_2	94	
" "	25	1	25 c.c. 0.8 per cent. NaCl+15 c.c. 3 per cent. H_2O_2	90	
" "	25	1	40 c.c. 0.8 per cent. NaCl+0.5 gm. glucose	96	
" "	25	1	40 c.c. 0.8 per cent. NaCl+0.5 gm. glucose	90	
" "	25	1	40 c.c. 0.8 per cent. NaCl+15 gm. glucose	94	
Cat's blood	50	1	Perfused through liver for thirty minutes before addition of phenolsulphone-phthalein	100	Blood+phthalein stood thirty hours
Dog's blood	50	1	Aërated with CO for 15 hours	95–96	
Cat's blood and liver	Whole	1	Blood perfused through liver two hours	45	
Cat's blood and kidneys	"	1	Blood perfused through kidneys 2.5 hours	95	
Rabbit liver	32	1	64 c.c. 0.8 per cent. NaCl+0.25 gm.glucose	79	
Monkey liver	26	1	50 c.c. 0.8 per cent. NaCl+0.25 gm.glucose	39	
Beef liver	50	1	Undiluted at 5° C.	52	
" "	30	1	Undiluted at 25° C.	33	
" "	30	1	Undiluted at 35° C.	26	
" "	30	1	Undiluted at 25° C.+0.5 gm. glucose	25	
Beef pancreas	30	1	Undiluted	82	
Cat's muscle	25	1	Undiluted mash	38	
Cat's intestine	25	1	Undiluted mash	34	
Cat's liver	25	1	Undiluted mash	0	
Sheep's spleen	50	1	Undiluted mash	90	

REFERENCES

1. Woodyatt, R. T., Sansum, W. D., and Wilder, R. M.: "Prolonged and Accurately Timed Intravenous Injections of Sugar," Jour. Amer. Med. Assoc., 1915, lxv, 2067–2070.
2. Rowntree, L. G., Hurwitz, S. H., and Bloomfield, A. L.: "An Experimental and Clinical Study of the Value of Phenoltetrachlorphthalein as a Test for Hepatic Function," Bull. Johns Hopkins Hosp., 1913, xxiv, 327–342.
3. Whipple, G. H., Peightal, T. P., and Clark, A. H.: "Tests for Hepatic Function and Diseases Under Experimental Conditions. Phenoltetrachlorphthalein," Bull. Johns Hopkins Hosp., 1913, xxiv, 343–357.

EFFECTS OF RETENTION IN THE KIDNEY OF MEDIA EMPLOYED IN PYELOGRAPHY*

WILLIAM F. BRAASCH AND FRANK C. MANN

With the recognition of the diagnostic value of pyelography came the realization that the method was not without danger to the patient. Deaths which were evidently the direct result of pyelography were reported by various observers. Animal experimentation demonstrated that death might follow the introduction of colloidal silver solution into the renal pelvis with overdistention. The introduction of the medium by means of gravity so as to obviate the danger of overdistention reduced the possibility of renal injury to a great degree.

In 1913 one of us[1] reported several cases of hydronephrosis removed at operation in which necrosis of the renal cortex was evident, although the pelvis had not been overdistended. It was believed that secondary retention of colloidal silver in the renal pelvis without overdistention could cause necrosis in the renal parenchyma. This observation was later corroborated by Krotoszyner[2] and by Keyes and Mohan,[3] who reported similar clinical observations. Keyes and Mohan further demonstrated the process conclusively by injecting a small amount of colloidal silver into the renal pelvis of dogs and then ligating the ureter. The kidneys removed later showed numerous areas of cortical necrosis as the result of the retention of the colloidal silver. From a histologic study of the areas of resulting necrosis it was evident that the minute particles of metallic silver deposited in the parenchyma were the underlying cause of the necrosis.

The avenues of introduction of the metallic deposits have not been definitely determined. It has been argued that the silver deposits found in the tubules reached the glomeruli primarily by means of lymphatic and vascular absorption, and were later secreted into the tubules. The histologic evidence advanced in support of this theory is hardly

conclusive. It would seem logical to hold that when the natural drainage of the renal pelvis is occluded, peristaltic contraction may force the pelvic contents into the tubules. Microscopic examination of any of the different solutions of colloidal silver employed in pyelography will show the presence of undissolved particles of metallic silver; a perfect solution is hardly possible, a fine suspension being the medium employed. The silver deposited in the renal substance acts like any other foreign body in that it causes suppuration and necrosis of the adjacent tissue. .With multiple deposits of metallic silver with adjacent foci of infection the resulting condition is practically that of an acute septic nephritis. As might be expected, clinical symptoms and resulting fatality are identical with acute septic nephritis. Necessarily, the indications for surgical treatment are similar in both conditions. Nephrectomy is indicated if the patient has a persistent high temperature and evidence of severe intoxication, which usually marks this condition following pyelography. That such a complication will occur in a comparatively small percentage of cases of hydronephrosis following pyelography made with proper technical precaution is evidenced by the fact that in more than 5000 cases at the Mayo Clinic in which pyelography was employed marked focal necrosis was found in but eight cases. In all of these the kidney was found to be actively secreting, although the drainage was temporarily interfered with. Less reaction followed when the substance of the kidney was largely destroyed. No deaths occurred which could be attributed directly to pyelography. However, the element of danger which is present in spite of every precaution would necessarily restrict its employment.

To prevent pyelography from falling into disuse as a method of diagnosis because of the possible danger involved in its employment, various forms of silver have been tried. Among the different media suggested, silver iodid in emulsion[4] and silver iodid in suspension[5] have been found less harmful in their effect. Although the frequency of focal necrosis was thus unquestionably diminished, it was not entirely eliminated. Two severe cases of focal necrosis following the retention of silver iodid injected into a hydronephrosis came under our observation. Moreover, the silver iodid suspension causes considerable local irritation. The injection of so viscid a substance as silver iodid emulsion with a syringe is objectionable because of the difficulty of gaging the degree of pressure in its introduction and the amount necessary for pelvic distention. The latest medium suggested, namely,

thorium,[6] evidently obviates many of the objections to those previously used, and has the following advantages: (1) It is in actual solution and not suspension; (2) it does not cause local irritation; (3) it can be introduced by means of gravity.

Thorium nitrate solution offers the safest medium for pyelography. Unfortunately, it casts a less distinct shadow than the colloidal silver preparations in common use. Further, it does not bring out the details of the calyces nor of the ureter as well as the silver preparation. It is peculiar that solutions of greater concentration (20 per cent.) cast no denser shadow than those of a lesser concentration (10 or 15 per cent.).

That focal necrosis may occasionally occur following the use of thorium was evident in a case of hydronephrosis which recently came under our observation. Microscopic examination of the tissue of the kidney removed showed numerous areas of round-cell infiltration such as are usually the result of infection. No evidence of metallic deposit was visible. The infection was predominant in the tissues about the tubules and but few glomeruli were involved.

Prior to the use of pyelography the diagnosis of renal urinary retention was usually arrived at by means of the ureteral catheter and the overdistention method. Following simple ureteral catheterization we have observed the presence of a considerable degree of focal suppuration in several kidneys subsequently removed at operation. Microscopic examination of these areas showed that they were of bacterial origin. It is quite impossible to introduce either a ureteral catheter or bland fluid into the renal pelvis which has insufficient drainage without danger of subsequent infection. However, the exercise of every precaution to keep such a catheter and the medium introduced sterile will somewhat reduce the number of cases of infection, but will not exclude them. We are under the impression that the focal necrosis and areas of suppuration noted in the case with thorium retention were the result of coincident bacterial infection. The use of opaque media, as in pyelography, should not bear the entire blame for cortical necrosis. Moreover, the kidney in which focal necrosis results following retention is primarily a "surgical kidney," and its sacrifice will not usually alter the necessary procedure. As a matter of precaution it is advisable always to ascertain whether the other kidney is functionating properly before catheterization, fluid overdistention, or pyelography is attempted in a case in which pelvic retention is suspected.

The object of the following series of experiments which were begun

in April, 1914, was to study the comparative effect of retention in the kidney of the various media used in pyelography and to determine whether the retention of chemical irritants in the pelvis of the kidney would produce lesions of that organ. This was accomplished by either a complete or partial occlusion of the ureter of a dog after injecting the substance into the pelvis of the kidney. The routine technic was to expose the ureter, usually the right, through a lumbar incision and carefully dissect it free for a short distance, about two inches, from the kidney. When the occlusion was made complete, the free portion of the ureter was ligated and the solution injected through it into the pelvis. The ureter was again ligated proximal to the entrance of the needle and sectioned between the ligatures. When a partial occlusion only was made the ligature was tightened over the needle at the point where it entered the lumen of the ureter. As the results did not materially differ, all the experiments will be reported together.

The capacity of the dog's kidney varies, but is practically always greater than 1.5 c.c. In order to avoid immediate distention of the pelvis, only 1 c.c. was used. After injecting and ligating the ureter it was replaced and the wound carefully closed. The specimens were obtained at various times after injection, but were approximately the same for the different substances used.

The effects of retention of the following substances were studied experimentally: (1) One per cent. solution of sodium chlorid; (2) saturated solution of boric acid; (3) saturated solution of sodium citrate; (4) methylene-blue; (5) 5 per cent. collargol; (6) 25 per cent. collargol; (7) 25 per cent. argyrol; (8) 25 per cent. cargentos; (9) washed staphylococci; (10) emulsion of silver iodid; (11) silver iodid in quince-seed emulsion; (12) 15 per cent. thorium nitrate neutralized; (13) 20 per cent. solution of thorium nitrate as used clinically; (14) 20 per cent. solution of thorium nitrate unneutralized. In many of these experiments the uninjected kidney was also studied.

In studying the kidney it was necessary to differentiate three distinct conditions: (1) The effect of the hydronephrosis; (2) the effect of the infection; (3) the effect of the retained substances. The effect of the hydronephrosis on the substance of the kidney could easily be distinguished. However, it was not always possible to determine whether the condition found in the kidney was due to an infection, to the retained substance, or to both.

Grossly, the kidney usually presented a degree of hydronephrosis

depending on the length of time after ligation.   The fluid which escaped
from the pelvis was quite often very turbid, and it was often possible to
find some of the injected solution.   In a few cases there was a necrosis
of the ureter at the point of ligation, with the formation of a perinephritic
cyst.

The capsule was usually thickened.   On section the renal substance
was thin and firm.   Quite often it was not possible to demonstrate
grossly any changes in the substance of the kidney due to the injected
solution.   However, in some instances there were pin-point hemor-
rhagic areas or small abscesses.   These were usually in the cortex near
the surface.   In two instances the medulla was stained throughout with
the injected substance.   The pelvic mucosa practically always showed
changes.   These consisted of hemorrhagic spots or areas of necrosis.
The mucosa was usually stained with injected solution, and some of the
substance could be scraped from the surface.   The results of the micro-
scopic study are as follows:

No.	Solution	Time	Change
1	Methylene-blue	10 days	None.
2	Methylene-blue	26 days	Slight. A few areas show infiltration.
3	Methylene-blue	15 days	None.
4	Methylene-blue	22 days	None.
5	Methylene-blue	12 days	Moderate. Several areas of focal inflamma-tion. Infection?
6	5 per cent. collargol	15 days	Marked. Entire medulla infiltrated; areas of necrosis; several cortical areas of pig-mentation.
7	5 per cent. collargol	9 days	Moderate. Several areas of infiltration of deeply staining cells.
8	5 per cent. collargol	25 days	Marked. Many areas of pigmentation defi-nitely organized throughout the remaining renal substance.
9	5 per cent. collargol	15 days	Slight. A few areas of infiltration.
10	5 per cent. collargol	8 days	Moderate. Several areas of necrosis.
11	5 per cent. collargol	7 days	None.
12	5 per cent. collargol	14 days	Slight. Several areas of infiltration of deeply pigmented cells in the cortex.
13	25 per cent. collargol	25 days	Marked. Entire remaining renal substance infiltrated. Few normal cells left. Many areas of necrosis.
14	25 per cent. collargol	30 min.	Very slight.
15	25 per cent. collargol	7 days	Slight. Many cells of the collecting tubules pigmented.
16	25 per cent. collargol	7 days	Slight infiltration of the pelvic mucosa.
17	25 per cent. collargol	4 days	None.
18	25 per cent. argyrol	22 days	Marked. Infiltration of all the remaining renal substance.
19	25 per cent. argyrol	5 days	None.
20	25 per cent. argyrol	24 days	Moderate. Marked infiltration with several areas of necrosis.

No.	Solution	Time	Change
21	25 per cent. argyrol	15 days	Slight. A few areas of pigmentation.
22	25 per cent. argyrol	8 days	Very slight.
23	25 per cent. argyrol	7 days	None.
24	25 per cent. cargentos	30 days	Marked. Many areas of pigmentation scattered throughout the remaining renal substance.
25	25 per cent. cargentos	13 days	Moderate. Many areas of pigmentation found mainly in the medulla.
26	25 per cent. cargentos	30 days	Marked. Remaining renal substance infiltrated. Many areas of necrosis.
27	25 per cent. cargentos	5 days	Slight. Several collecting tubules contain the brown-colored substance. Pelvic mucosa is infiltrated.
28	25 per cent. cargentos	7 days	Slight. A very few areas infiltrated with deeply staining cells.
29	25 per cent. cargentos	7 days	None.
30	Silver iodid	24 days	None.
31	Silver iodid	15 days	None.
32	Silver iodid	16 days	Moderate. Marked infiltration.
33	Silver iodid	7 days	None.
34	Silver iodid	12 days	Very slight.
35	Emulsion silver iodid with quince seed	7 days	Very slight.
36 ·	Emulsion silver iodid with quince seed	7 days	Very slight.
37	Emulsion silver iodid with quince seed	9 days	None.
38	Emulsion silver iodid with quince seed	58 days	No renal structure left.
39	Emulsion silver iodid with quince seed	9 days	None.
40	Washed staphylococci	3 days	Slight. A few abscesses.
41	Washed staphylococci	2 days	Marked. Many abscesses.
42	Washed staphylococci	5 days	Moderate. A few abscesses.
43	15 per cent. thorium nitrate	4 days	None.
44	15 per cent. thorium nitrate	9 days	None.
45	15 per cent. thorium nitrate	14 days	None.
46	15 per cent. thorium nitrate	6 days	None.
47	15 per cent. thorium nitrate	10 days	Slight.
48	1 per cent. NaCl	4 days	None.
49	1 per cent. NaCl	10 days	None.
50	Saturated solution, boric acid	10 days	None.
51	Saturated solution, boric acid	6 days	None.
52	20 per cent. solution thorium nitrate	10 days	Microscopic picture: Acute infection. Renal substance infiltrated throughout; complete loss of normal structure in many areas. Definite abscesses in some areas.
53	20 per cent. solution thorium nitrate	6 days	Marked. Substance of kidney infiltrated throughout. Definite abscesses in some areas. Tubules mostly disappeared or badly damaged. Glomeruli seem less affected than tubules.

No.	Solution	Time	Change
54	20 per cent. solution thorium nitrate	7 days	None.
55	20 per cent. solution thorium nitrate	4 days	Slight.
56	Saturated solution sodium citrate	7 days	A few small subcortical infiltrations which appear to be beginning abscesses.
57	Saturated solution sodium citrate	4 days	None.
58	20 per cent. solution thorium nitrate	3 days	None.
59	20 per cent. solution thorium nitrate	3 days	None.
60	Saturated solution sodium citrate	3 days	Slight. There are a few areas of beginning infiltration.
61	20 per cent. solution thorium nitrate	3 days	Slight. There are a few areas of beginning infiltration.
62	20 per cent. solution thorium nitrate	7 days	None.
63	20 per cent. solution thorium nitrate	7 days	Slight. There are a few beginning areas of infiltration.
64	20 per cent. solution thorium nitrate	3 days	Moderate. There are a few very large areas of infiltration in the cortex.
65	Saturated solution sodium citrate	7 days	None.
66	20 per cent. solution thorium nitrate (unneutralized)	2 days	Moderate. There are some areas of cortical infiltration.
67	20 per cent. solution thorium nitrate (unneutralized)	2 days	Moderate. There are a few areas of beginning infiltration.

An attempt was made to estimate the changes due to the injected solution. These changes varied, but in general they consisted of areas of focal necrosis with or without actual demonstration of the localized substance. These areas were usually located in the cortex but have been found in the medulla. The lesion appears to consist of an accumulation of the substance in the tubules of the kidney. We have not definitely determined whether the substance reaches the cortex through the tubules or by way of the blood and lymphatic vessels. Observations tend to show that in some instances either route may be followed. In a few instances lesions of the uninjected kidney have proved that the substance was absorbed and excreted. The lesions which follow excretion of the substance are usually located in the medulla. These are characterized by infiltration of large, deeply staining cells. When organization takes place there is first formed an area of necrosis and hemorrhage in the immediate vicinity of the substance. Later a definite wall of connective tissue forms, with absorption of the necrotic material. In many instances infection followed the localization of the substance

so that it was impossible to differentiate the condition from a primary infection.

RESULTS

The results of these experiments are tabulated briefly as follows:

1. The injection of 1 per cent. solution of sodium chlorid and a saturated solution of boric acid in two experiments each did not produce a lesion of the kidney.
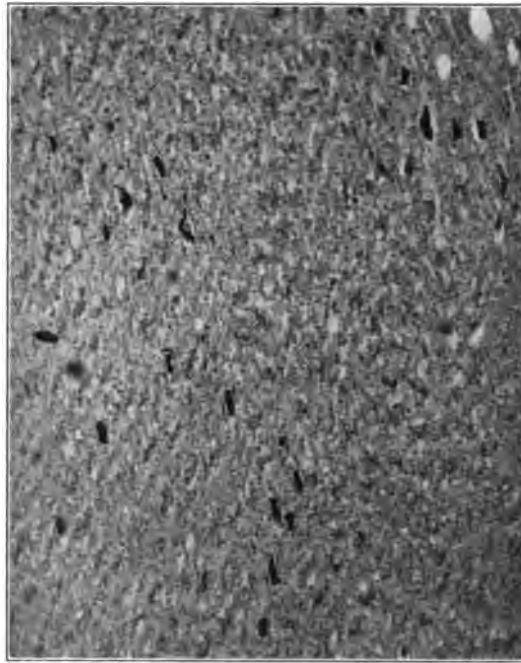
Fig. 188.—Experiment 27. Photomicrograph (× 50) showing cargentos in kidney tubules five days after injection.

2. The injection of a saturated solution of sodium citrate in four experiments produced lesions in two instances. The cultures of tissue were negative for bacteria in both of these positive experiments, and in one only were a few micrococci found in the fluid of the pelvis.

3. In the five experiments in which methylene-blue was injected only one kidney showed a slight lesion. This lesion may have been due to an infection.

4. In seven experiments 5 per cent. collargol was injected. Lesions of various degrees of severity occurred in six.

5. In the five experiments in which 25 per cent. collargol was injected, lesions were found in four.

6. The injection of 25 per cent. argyrol in six experiments produced lesions in four.

7. The injection of 25 per cent. cargentos in six experiments produced lesions in four.
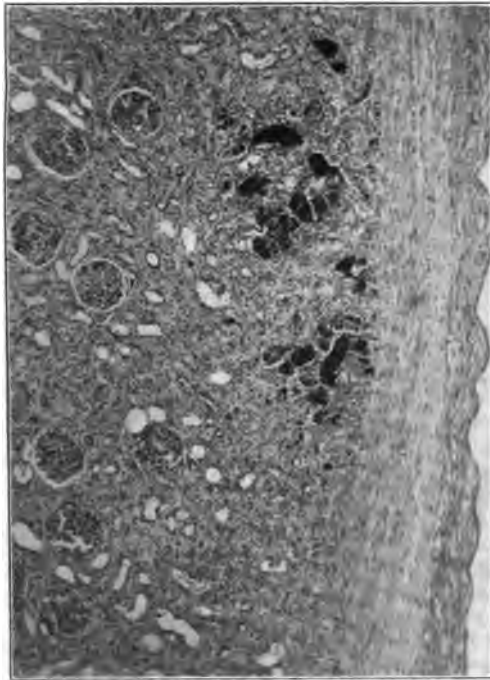
Fig. 189.—Experiment 6. Photomicrograph (× 60) showing collargol in the kidney tubules fifteen days after injection.

8. In five experiments in which silver iodid was injected, moderate lesions were noted in two.

9. In five experiments in which silver iodid with quince seed was injected, slight lesions were found in two.

10. In five experiments 15 per cent. thorium nitrate was injected. A slight lesion was noted in one kidney.   In order to test this substance to a greater extent, in one experiment the pelvis of the kidney was overdistended with 5 c.c. of the solution and in another 2.5 c.c. were injected. The first specimen was examined after four days and the latter after

fifteen days. In neither were any changes noted which could be attributed to the injected solution.

11. The injection of a 20 per cent. solution of thorium nitrate, neutralized as used clinically, in ten experiments, produced lesions of various degrees of severity in five. In two of these the kidney was very badly damaged. It is suggestive that in these two experiments the solution was used immediately after it had been made. It is possible
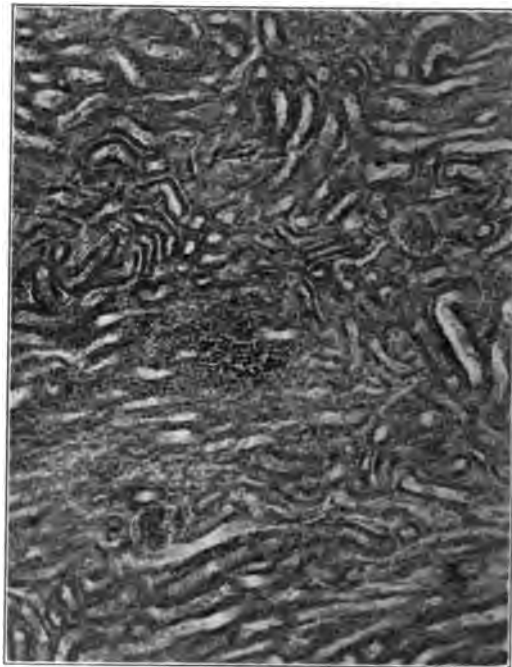
Fig. 190.—Experiment 25. Photomicrograph (× 60) showing a localized area of cargentos thirty days after injection.

that an old solution is better than one just freshly prepared. In the other three experiments in which lesions occurred the cultures of tissue and smears of the pelvic fluid were negative for bacteria.

12. The injection of 20 per cent. solution of thorium nitrate, unneutralized, in two experiments, produced lesions, particularly of the pelvis, in both. Smears of the pelvic fluid were negative in both of these experiments, and cultures of tissue showed a few staphylococci, possibly a contamination.
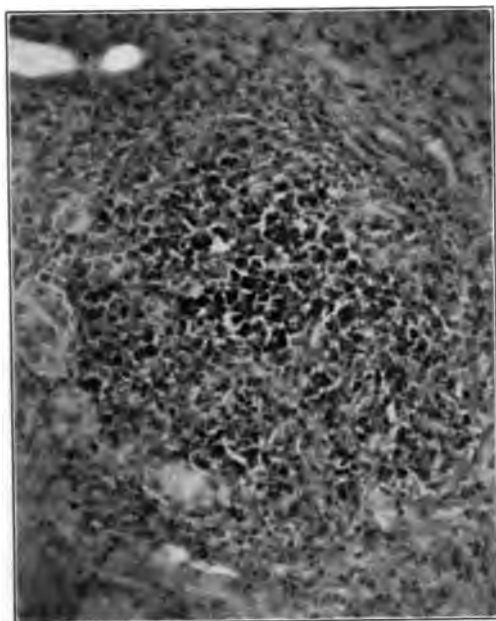
Fig. 191.—Experiment 25.   Photomicrograph ($\times$ 200) showing a higher magnification of one of the areas in Fig. 190.
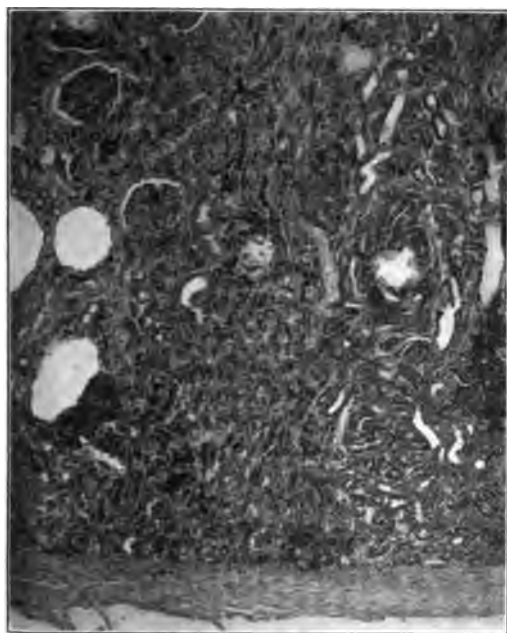
Fig. 192.—Experiment 47.   Photomicrograph ($\times$ 50) showing some areas of infiltration in the periphery of cortex ten days after the injection of thorium nitrate.

'16—24

CONCLUSIONS

Conclusions Derived from Clinical Data.—1. The greatest danger in the use of silver preparations is their retention in actively secreting kidneys.

2. With multiple foci of necrosis the condition should be regarded as a septic nephritis and immediate nephrectomy is indicated.
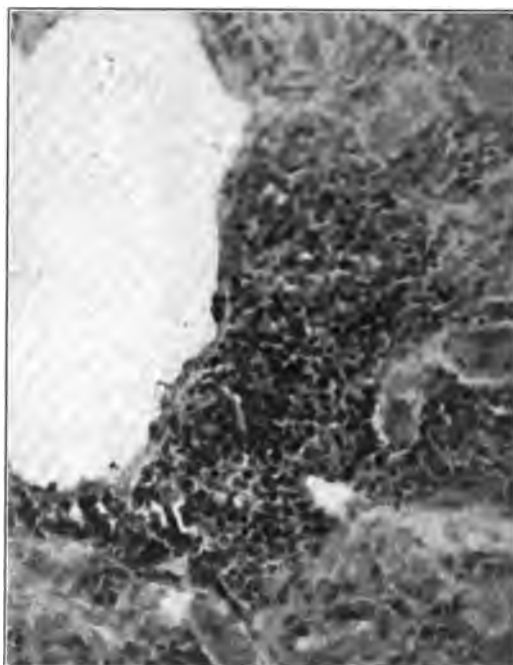
Fig. 193.—Experiment 47. Photomicrograph (× 225) showing higher magnification of one of the areas in Fig. 192. It is impossible to tell what part the solution played in its formation. It appears to be a primary infection.

3. Focal necrosis as the result of infection may follow the introduction of a ureteral catheter or of bland fluids into a pelvis with insufficient drainage.

4. Silver iodid suspensions are less harmful than the colloidal silver preparations.

5. Thorium nitrate in 10 or 15 per cent. solutions causes the least reaction but casts a less distinct shadow.

Conclusions Derived from Experimental Data.—1. Mild chemical

irritants, as sodium chlorid and boric acid, when injected and retained in the pelvis of the kidney, do not produce lesions of that organ.

2. The effect of methylene-blue was practically negligible.

3. More stringent chemical irritants, as sodium citrate and 20 per cent. thorium nitrate, when tested in the same drastic manner, produce lesions of the kidney, which seem directly due to the chemical injected, and not to any concomitant or subsequent infection.

4. Argyrol, collargol, and cargentos were about equally responsible for producing the most marked changes noted. It was often possible to find areas in which the metal could be distinguished.

5. The weaker solutions of colloidal silver did not appear to be less harmful than a more concentrated solution.

6. The silver iodid preparations produced less change in the kidney than the other silver solutions. Of the two preparations of silver iodid, the one in which it is suspended in quince-seed emulsion caused the least necrosis.

7. So far as we have been able to determine by the method employed, thorium nitrate (15 per cent. solution) did not produce changes in the kidney except possibly in one experiment. Care must be taken in its preparation that the solution is thoroughly neutralized.

REFERENCES

1. Braasch, W. F.: "Recent Progress in Ureteropyelography," Jour. Michigan Med. Soc., 1913, xii, 189–190.
2. Krotoszyner: "Untoward Results of Pyelography," Surg., Gynec. and Obst., 1914, xix, 522–527.
3. Keyes, E. L., and Mohan, H.: "The Damage Done by Pyelography," Amer. Jour Med. Sci., 1915, cxlix, 30–41.
4. Kelly, H. A., and Lewis, R. M.: "Silver Iodide Emulsion—a New Medium for Skiagraphy of the Urinary Tract," Surg., Gynec. and Obst., 1913, xvi, 707–708.
5. Young, E. L.: "A New Preparation for Pyelography," Boston Med. and Surg. Jour., 1915, clxxii, 539–544.
6. Burns, J. E.: "Thorium, a New Agent for Pyelography. Preliminary Report," Jour. Amer. Med. Assoc., 1915, lxiv, 2126–2127.

CLINICAL DATA OF NEPHROLITHIASIS*

WILLIAM F. BRAASCH

From January 1, 1898, to January 1, 1916, 450 patients were operated on at the Mayo Clinic for nephrolithiasis. The total number of operations, including those for recurrence and bilateral stone, was 484. A review of the clinical records, both preoperative and postoperative, gives data of considerable interest.

Identification of Shadows in the Roentgenogram.—It was not long ago that surgical explorations were made for renal stone because of a history of pain referred to the region of the kidney. To-day the surgeon would rarely make such an exploration without previous x-ray examination. However, although we depend on the x-ray for our diagnosis of renal stone, an increasing reaction has developed against its infallibility in recent years. It has frequently happened that the roentgenogram has shown a shadow which appeared to be stone, but at operation no stone was found. It has also happened that no shadow has appeared in the roentgenogram, and at operation even large stones were found. It is now well recognized that the roentgenogram may lead to considerable diagnostic error unless its interpretation is aided by cystoscopic and allied data. The mistakes are principally of two types: (1) Error in interpretation, and (2) failure to show the stone shadow. Error in interpretation has been largely eliminated through the aid derived from the cystoscope and particularly from pyelography. Failure on the part of the x-ray to show a shadow still persists in a small percentage of cases but it is usually the result of error in roentgenographic technic. Interpretation of the roentgenogram without complete clinical and cystoscopic data is inaccurate, and operation based on such evidence alone is not good surgery.

Localization of Stone.—The localization of the stone is of as much importance in the diagnosis as the identification. It is obvious that if

exact localization is made prior to operation, the removal of the stone is facilitated, first, by guiding the operator in his search, and, second, by suggesting the most feasible method of procedure. When the shadow is large (an inch or more in diameter) the surgeon does not, as a rule, have much difficulty in finding the stone; when, however, it is smaller, considerable difficulty may arise in finding the stone in the kidney which usually becomes congested and enlarged when brought to the surface. The exact situation of a stone in the kidney is often difficult to determine in the original roentgenogram. By outlining the renal pelvis in a pyelogram and then comparing it with the position of the stone shadow, the stone can be localized more accurately than in the ordinary roentgenogram. The main problem in the localization of the stone is to determine whether it is situated in the true pelvis, in a calyx, or in the cortex. If situated in the pelvis, the shadow may be obscured by the pelvic outline and the exact position can be determined only by comparing the pyelogram with the original roentgenogram. Frequently, however, the outline of the stone is visible through that of the pelvis. When the stone is situated in a calyx, its outline may be seen through that of the calyx, which is usually characterized by definite deformity. When the stone is in a calyx, the comparative size of the calyx may be ascertained and this may be of value in determining the possibility of removing the stone through the pelvis. When the stone is situated partially in a calyx, and partially in the cortex, its outline may be seen extending beyond that of the calyx. When situated in the cortex, the stone may be seen clear of the pelvic outline.*

It is also true that when the stone is very small, say less than one centimeter in diameter, the question may well arise whether it should be considered as surgical. Since when in the pelvis or calyces a large proportion of such small stones are passed spontaneously, it is usually better to postpone operation unless the symptoms become severe or some complication arises. Even when the stone has been localized in the cortex, it is often advisable, in the absence of marked symptoms, to await a moderate degree of increase in its size. The mutilation of the kidney substance in the search for a very small stone may cause considerable permanent destruction of the tissue.

Situation of the Stone.—Exact localization of the stones was impossible in many of the cases of nephrectomy because of the wide-spread destruction of tissue, but as far as could be ascertained the number of stones

* For further data see Braasch, W. F. Pyleography, Chapter VII.

situated in the pelvis and cortex was about equal. Stones other than those found on nephrectomy were located as follows: 180 in the pelvis; 14 in the pelvis and calyces; 12 in the pelvis and cortex; 20 in the calyces; 48 in the cortex; and 8 at the ureteropelvic juncture. Since stones found in the calyces and at the ureteropelvic juncture are in portions of the pelvis, we have a total of 222 (78 per cent.) cases with pelvic stone. The number of cortical stones was 60 (21 per cent.).

Multiple Stones.—Renal stone was found to be single in 285 operations and multiple in 188. The large proportion of the multiple stones may be explained, in a measure, by the fact that with most of the patients of this group the symptoms were of long duration. The several stones usually form at different intervals over a period of years, and it is evident that this process, together with destruction of the kidney, could be largely prevented by early operation. Multiple stones occurred in 124 cases of pyonephrosis requiring nephrectomy, and the consequent renal destruction prevented exact localization. In many cases of the group in which the stones were localized in the cortex they evidently occurred secondary to larger pelvic stones. The location of the multiple stones in the other operations was as follows: pelvis, 24; calyx, 6; cortex, 16; pelvis and calyx, 10; pelvis and cortex, 8. From this it may be inferred that when stones are multiple they occur more frequently in the pelvis and calyces than in the cortex. Destruction of the kidney tissue was found to such an extent in 126 patients that nephrectomy was necessary. The other operations required for the removal of the multiple stones were as follows: pelviolithotomy 34, nephrolithotomy 14, combined pelviolithotomy and nephrolithotomy 14. In many cases in which multiple stones were found at operation, only a single shadow was present in the roentgenogram previously made; in others there was one definite shadow together with one or more other shadows which could not be definitely interpreted as due to stone. In many instances it was necessary to make a very careful search of the entire kidney in order to find the various stones. Therefore, we should not always be content with the roentgenographic evidence as to the number of stones present, and the surgeon should make a careful search for more than one stone even though the roentgenogram may show only a single shadow. It is probable that in many cases reported as recurrence of renal stone one or more stones were not found at the time of the first operation and the remaining stones were regarded as recurrences.

Coincidence of Stones in the Kidney and Ureter.—A stone was found

in the ureter and the kidney on the same side in 26 patients (5.7 per cent.). This is of interest as it indicates the necessity of plates showing both the kidney and the entire ureter. When there is a definite stone shadow in the area of the kidney, a small shadow in the ureter may be easily overlooked. The data derived from the cystoscopic examination, ureteral catheter, and pyelo-ureterogram are frequently necessary to identify a shadow of this kind. There was nothing in the histories of the patients to suggest multiple localization. The question frequently arises as to the best method of surgical procedure in this complication. Whether or not the stone in the ureter should be removed first depends largely on the degree of function in the affected kidney. If, on cystoscopic examination, it is found advisable to save the kidney, it is usually well to remove the ureteral stone first. When the function of the kidney is largely destroyed, nephrectomy is indicated as the primary procedure. When a large irregular stone remains in the ureter, it is advisable to remove it at a secondary operation. When the stone is small, however, and the ureter is not extensively dilated, it may not be necessary to remove the stone at all. When there is considerable dilatation of the ureter due to the stone, it may be advisable to perform a ureteronephrectomy. As a rule, no urinary leakage from the bladder by way of the remaining ureter will develop even though the ureter is greatly dilated. We have observed two cases, however, in which this has occurred and necessitated subsequent ureterectomy. Also, occasionally, when a thick, dilated, and infected ureter is left, a fistula discharging a small amount of thick pus may persist and necessitate subsequent ureterectomy.

Branched Stone.—Seventy-six stones were described as being distinctly branched. Counting only operations other than nephrectomy where exact localization was not possible, the stone was found in the pelvis and calyces in 22 cases and in the substance of the kidney in 14. It is evident, therefore, that branched stones are found more frequently in the pelvis and calyces than in the cortex. As a rule, branched stones found in the pelvis are much larger than those in the cortex and follow the outline of the various calyces. Even though a branched stone almost fills the pelvis, it may cause few symptoms, since it may not alter its position so as to interfere with the urinary excretion. The branched stone is frequently soft, casts a very dim shadow in the roentgenogram, and at operation often crumbles into a sand-like substance. Not infrequently what appears to be a single branched stone in the roentgeno-

gram proves at operation to be made up of numerous smaller parts which are so grouped as to give the appearance of a single branched stone. The amount of renal secretion remaining with a large branched stone is frequently amazing. There may be but little gross evidence of renal lesions in the urine, and but a few microscopic pus or red blood-cells. The various operations found necessary were as follows: nephrectomy, 40 cases (52 per cent.); pelviolithotomy, 16 cases (21 per cent.); nephrolithotomy, 14 cases (19 per cent.); and combined nephrolithotomy and pelviolithotomy, 6 cases (8 per cent.).

Bilateral Stone.—Bilateral occurrence of stone was noted in 48 patients—9.9 per cent. of the total number operated on. This, however, does not represent the entire number of cases of bilateral stones examined at the Mayo Clinic. Up to 1916 the clinical records show that 24 patients with bilateral nephrolithiasis were examined, but not operated on. A large proportion of this number were regarded as better off without operation because of the absence of subjective symptoms or the large size of the stones. A smaller number was found to be inoperable because of the advanced destruction of the kidney or secondary infection. The symptoms were not regarded as being sufficiently severe to require operation. If we were to include all cases in which the diagnosis was evident but in which no operation was performed, the percentage of bilateral occurrence would be considerably higher—approximately 15 per cent. of the total. At operation the stones were found situated as follows: In the cortex on both sides in 10 cases; in the cortex on one side and in the pelvis on the other in 14 cases; in the pelvis on both sides in 10 cases (in the kidney on one side and in the ureter on the other, 3 cases); and in the pelvis on one side associated with pyonephrosis on the other in 14 cases.

Previous Operations.—One hundred and forty-three patients, or practically one-third of the total number, had had previous laparotomies performed elsewhere for relief of pain. Of this number, 83 had stone in the right kidney, 55 stone in the left kidney, and 5 bilateral stone. It is evident that laparotomy was performed more often for stone in the right kidney than for stone in the left. It is of interest that 21 of the patients with stone in the left kidney had had previous operations on the appendix or gallbladder.

Previous operations on the kidney done elsewhere were recorded in 23 cases. The operations were nephrectomy, partial or complete, 13 cases; nephrotomy 7 cases; pelviolithotomy 3 cases. At the time of

the secondary operation the kidney was found to be so largely destroyed in 14 cases as to indicate nephrectomy. After previous operation done elsewhere a fistula persisted in 12 patients and in every case nephrectomy was found necessary. A fistula persisted in 3 patients following operation at the Mayo Clinic.

Passed Stone.—Fifty-three of the patients gave a definite history, and 14 a somewhat questionable history, of having passed a stone from the kidney prior to the operation. Eight described the pain at the time of passing the stone as being on the side opposite the kidney operated on. Seven patients evidently had passed stones from both kidneys. In the majority of cases the stone was probably passed from the same side as that operated on. A single stone was passed in 23 cases, and more than one stone in 30 cases, which indicates that the passage of multiple stones is more frequent and is suggestive of a stone-forming tendency in the kidney.

At operation of those who had passed multiple stones (30) a single stone was found in 15 patients and multiple stones in 15. Of those who has passed single stones (23), single stones were found at operation in 16 and multiple stones in 7. From this it may be inferred that when multiple stones have been passed the chance of finding stones at operation is greater than when single stones have been passed. As to the type of operation in this group, a nephrectomy was found necessary in 18 cases, nephrolithotomy in 18 cases, and pelviolithotomy in 16 cases.

Type of Operation.—The operations performed were divided as follows: nephrectomy in 188 cases; nephro-ureterectomy in 16; pelviolithotomy in 206; nephrolithotomy in 40; combined pelviolithotomy and nephrolithotomy in 34. The large proportion of cases in which nephrectomy was found necessary, 204 (41 per cent.), is of interest. Most of the cases in this group were diagnosed clinically as pyonephrosis and stone. In the other cases the amount of healthy tissue remaining was so little that nephrectomy was clearly indicated. The stone was described as multiple in 124 cases (66.7 per cent.) and single in 64 cases (33.5 per cent.). With single stones, the pyonephrosis, as a rule, is secondary to the stone formation. With multiple stone, the stones are frequently formed secondary to the inflammatory process. In many of these cases the duration of symptoms extended over a period of many years and the condition was either unrecognized or had remained dormant. Although the kidney was saved whenever it was possible,

nephrectomy was usually deemed advisable in the presence of wide-spread destruction of the kidney tissue.

That pelviolithotomy is the operation of choice, when possible, is demonstrated by the comparatively large number of patients on whom it was done. In some instances, although the stone was situated in the pelvis or calyces, either nephrotomy alone or combined with pelviotomy was preferable because of areas of tissue necrosis in the cortex requiring drainage. Removal of the ureter as well as the kidney was found necessary in 16 cases. In the majority of these there were one or more stones in the ureter with consequent marked dilatation and infection. It was feared that the dilated ureter might act as a diverticulum with secondary formation of stones or that it would become a focus of urinary infection. It is rare, however, that a ureter, even though markedly dilated, permits permanent reflux of urine from the bladder unless there is some malignant complication.

Perinephritic abscess was found in 10 cases. In 3 it was so extensive that preliminary drainage was first effected. In the others, however, nephrolithotomy or nephrectomy was done at the same time, usually the preferable procedure. This number does not include perinephritic involvements, such as fibrous adhesions or large deposits of inflammatory fat which are frequently found.

Mortality.—As nearly as could be ascertained, the total number of patients who have died since operation is 35. Of this number 3 died in the hospital because of the operation—an operative mortality of 0.6 per cent. It is of interest that no chemical estimate was made of the function of the remaining kidney, surgical judgment having been based on the grosser clinical findings together with careful cystoscopic and roentgenographic examination. The 3 deaths that occurred in the hospital followed nephrectomy for pyonephrosis and multiple stones. The symptoms were of long standing, and the patients were weakened and toxic as a result of the chronic infection. One died from septic pneumonia three weeks after operation, the second (an emergency case) from evident renal insufficiency, and the third died two weeks after operation with evidence of sepsis. It will be noted that there was no operative mortality following either nephrolithotomy or pelviolithotomy.

On reviewing the histories of the 32 patients who died subsequent to recovery from operation, it was found that 8 had bilateral nephrolithiasis. It is evident that the prognosis of bilateral stones is much

more unfavorable than that of unilateral stones. In most of the 8 cases death occurred within one or two years after operation.

There were 22 deaths following nephrectomy for pyonephrosis and stones. Practically all of the patients had had symptoms of long standing prior to operation and on clinical examination showed evidence of the chronic infection in other organs which evidently was the chief factor in shortening their lives.

As far as could be ascertained, the cause of death of the 32 patients was renal complications in 12 cases, and other causes in 7. In 13 instances the exact cause is not known, but was evidently not renal. Besides the 3 patients who died immediately following the operation, 14 died within one year after, 5 from two to three years after, and 7 more than three years after. In 6 instances the date of death is not known. The after-course of patients subsequent to the operation was as follows: 43 were reported alive and well more than ten years after operation; 121 more than five years after; and 110 more than two years after. The bulk of the operations, however, occurred within the last five years. The larger percentage of the subsequent deaths was due to renal complications, either bilateral nephrolithiasis, nephritis, or infection in the remaining kidney. The majority of the patients, as shown, died during the first year following operation.

Postoperative Results.—The frequency of the recurrence of renal stone has long been a disputed subject. Of considerable interest are the figures recently published by Cabot, who claims that among 66 patients previously operated on for renal stone at the Massachusetts General Hospital, and who were recently reëxamined, recurrence of stone was found to be 49 per cent. Because of the wide geographic distribution of the patients operated on at the Mayo Clinic, it is impossible to make a reexamination in every case. However, complete clinical data, including x-ray, urinalysis, etc., were obtained for 88 patients previously operated on for renal stone who returned to the Clinic for reëxamination. Of these 88 patients, 13 (14.7 per cent.) had recurrence. This percentage of recurrences, however, is manifestly higher than that in all patients operated on, since nearly all of those reëxamined had sufficiently definite symptoms to cause them to return.

In a large number of cases (75) the findings on reëxamination were negative, although many of the patients had definite aches and pains referred to either the renal area or the upper abdomen. From this it is very evident that positive subjective symptoms are not to be relied on.

Occasional pain referred to the kidney area following a renal operation is not uncommon, and may be explained either by functional causes or possibly a remaining renal infection, injury to a nerve, etc. Among the 75 negative cases, the roentgenogram showed a shadow in either the kidney or the ureter in 5 patients. These shadows, however, were definitely proved to be extra-renal and extra-ureteral by means of either careful cystoscopic and pyelographic examination or surgical exploration. It is evident, therefore, that the presence of roentgenographic shadows alone in the kidney cannot always be regarded as absolute evidence of the recurrence of stone.

The urine of 12 of 69 patients found negative on roentgenographic examination showed red blood-cells and pus-cells, usually but few in number. This indicates that a mild degree of infection frequently persists for a long period after the removal of the stone, and the question may well arise whether such infection is not the original etiologic factor. In the 13 positive cases urinalysis showed the presence of red blood-cells or pus-cells to a variable degree in every case.

Of the 13 patients in whom a recurrence was found, 11 were reoperated on. In every case but one the stones recurred in the same portion of the kidney as at the primary operation. In 2 instances the stone had been removed from the pelvis. In 1 it had been found in the cortex in the primary operation and the subsequent operation disclosed multiple recurrence with such destruction of the kidney that nephrectomy was necessary. Repeated recurrence requiring a third operation was noted with 2 patients only, the others remaining well after the second operation. In but 2 cases in which a nephrectomy had been done was recurrence noted in the opposite kidney. In other cases a small stone was passed from the opposite kidney shortly after the operation, and it may be assumed that it was present but undiscovered at the time of operation. As Cabot has suggested, the rarity of stone appearing in the opposite kidney subsequent to nephrectomy must be regarded as indicating that renal lithiasis is dependent on anatomic factors. That bilateral stones have no particular tendency to recur is evident from the small number of recurrences noted, i. e., 5 cases (11.9 per cent.).

In order to obtain information concerning the subsequent course of patients operated on for renal lithiasis and not reëxamined, letters of inquiry were sent out asking detailed questions as to exact location and severity and time of any recurring attacks of pain. Two hundred and eighty-seven replies were received. From these it was inferred that 241

patients should be regarded as negative, 15 had probable recurrence, and 18 had passed stone some time following the operation.

Although, judging from a review of the symptoms of the 450 patients operated on, absence of well-marked pain does not necessarily exclude the possibility of recurrence of stone, this group constitutes a very small proportion of the total. In order to make further study of a few patients with doubtful symptoms, specimens of their urine were obtained for examination. With but few exceptions these were negative.

Fifteen patients had symptoms sufficiently positive to make it probable that they had had recurrence, although we were unable to corroborate this by x-ray and cystoscopic examinations. With one exception specimens of urine contained pus- and blood-cells. It is of course probable that several of this group would show no recurrence on direct examination. This number would offset the possibility of error in the negative group.

Eighteen patients claimed to have passed stones following operation. In 4 cases, however, the pain was on the side opposite to that operated on. One patient had had a nephrectomy so that the recurrence must have been on the opposite side. Soon after the operation several patients passed stones which in all probability were missed at the time of the operation. Although such stones should not be regarded as recurrences, they have been included as such. Again it is probable that some of the "stones" were in reality slugs of mucus, etc. The addition of this entire number to the total of recurrences further offsets the possible percentage of error in the negative group. But 2 of this group required subsequent operation, so that although actual recurrence was probable, the group as a whole could not be regarded as having surgical recurrence. The fact that all patients who passed stone following operation had stone in the pelvis or calyces at the first operation bears out the contention previously made that recurrence usually takes place in that portion of the kidney where the stone was situated primarily.

Taking into account the number of patients whose x-ray examinations were positive (13), those with positive symptoms and urinalysis (15), and those with a history of having passed stones after operation (18), we have a total of 46 patients (9.8 per cent.) who may be regarded as having had recurrence of stone. This is a liberal interpretation of the statistics at hand. It may be safely stated, therefore, that with accurate preoperative diagnosis, operative technic, and judgment, the percentage of recurrence of renal lithiasis should be less than 10 per cent.

CLINICAL DATA OF POLYCYSTIC KIDNEY *

WILLIAM F. BRAASCH

Until recently the clinical diagnosis of polycystic kidney has been regarded extremely difficult and the occurrence of the disease rare. The majority of cases have been discovered at necropsy and reported from the records of large general hospitals. However, with increased knowledge and with the aid of recent methods of clinical examination, the condition is no longer looked upon as infrequent and may be recognized often clinically. This is particularly true in surgical clinics, where patients with surgical complications of polycystic kidney seek relief.

According to the records of the Mayo Clinic up to May 1, 1916, 41 patients had been operated on who, on exploration, were found to have polycystic kidneys. Twenty-six of these were recognized clinically.

Occurrence.—Kidd divides the course of the disease into three stages:

1. The latent stage necessarily occurring in the young adult and usually discovered only in the course of general abdominal exploration.

2. The stage of renal tumor and hematuria (usually found in surgical clinics in patients at middle adult life) and

3. The uremic stage (more commonly seen in the general hospital or medical clinics).

The early age of the majority of the patients in this series emphasizes the fact that polycystic kidney is usually discovered on surgical exploration in either the stage of latency or the stage of surgical complication. Only cases of the adult type have been included, since no case occurring in infancy was observed which could be regarded as surgical. Although the average age was forty-six years, 10 patients (25 per cent.) were below forty years of age. One of the 2 who were below thirty was only eighteen. On the other hand, 7 (17 per cent.) were sixty years or more, showing that because of an unusual degree of resistance the condition may not be recognized until surgical complications cause subjective

symptoms. No material difference in occurrence as to sex was noted. In regard to hereditary tendencies, the records are not complete, but definite evidence that heredity has an influence was noted in several instances. In one instance a history of cystic kidney was ascertained for two preceding generations.

SUBJECTIVE SYMPTOMS

The predominant subjective symptoms usually are pain, hematuria, tumor, or such symptoms as result from diminished renal function.

Pain.—Unless interference with urinary drainage or wide-spread infection occurs, the pain is not severe in character. Occasionally, however, a dull ache is referred to either loin, usually unilateral, which may be explained as due to an increase in the size of the cysts, which causes either pressure or increase of intrarenal tension. Interference with drainage resulting from blood-clots, lithiasis, and ureteral obstruction may be the cause of severe colic and mask the underlying condition.

Hematuria.—Hematuria occurred in 16 cases (40 per cent.). It was usually profuse, and continued over periods of from several days to several months. In 6 cases it was described as occasional, and in 8 as continued over a period of months. Hematuria is evidently caused by rupture of small blood-vessels in cysts, and the blood appears in the urine only when one of the cysts ruptures into the renal pelvis. When there is a history of recent hematuria, large cysts filled with dark bloody fluid or degenerated blood-clots of various hues may be found on surgical exploration. Hematuria is usually stopped by puncture of the blood-distended cysts. The severe colic frequently accompanying the condition is caused, as a rule, by clots, although overdistention of the cysts may also be a factor. Intracystic hemorrhage may be present without hematuria.

Evidence of Renal Insufficiency.—The clinical symptoms and data in cases of polycystic kidney in the stages of renal insufficiency may resemble those occurring in interstitial nephritis to such a degree that it has been argued the two conditions are practically identical. When clinical evidence suggests interstitial nephritis in young adults, it is advisable to examine carefully for evidence of bilateral renal enlargement. However, the clinical symptoms of renal insufficiency with polycystic kidney differ in many respects from those occurring with nephritis. In most instances the first evidence of renal disturbance,

and occasionally the only evidence during a period of several years, is nausea and vomiting. It was present in 6 of the 9 patients showing other clinical evidence of renal insufficiency. Cardiac disease occurred but infrequently, and is evidently a terminal complication. None of the patients had edema of the extremities.

Blood-pressure.—Blood-pressure records were available for but 16 patients; it was normal in 7. In the remaining patients the systolic blood-pressure was variably increased. In 1 case it rose as high as 240, and the diastolic pressure as high as 180. Two of the 4 patients with a systolic pressure of more than 200 died as a result of operation. The question may well be raised whether any operation will materially influence or permanently reduce a very high blood-pressure. In three of the patients with high blood-pressure examined subsequent to operation the blood-pressure was decreased but little. An extremely high systolic and diastolic blood-pressure with a specific gravity as low as 1003 or 1004 and but a trace of phthalein contra-indicates even a Rovsing operation.

Urinary Data.—The specific gravity in 17 of the 41 cases was 1015 to 1031; in 14 cases, 1010 to 1015; in 9 cases, below 1010.

Low specific gravity and polyuria are to be expected with polycystic kidney in the stage of present or impending renal insufficiency. In other stages it is not necessarily present, and a normal specific gravity does not exclude polycystic change. It is of interest that all but one of the patients with a specific gravity below 1010 have been reported dead, and these constitute all of the deaths so recorded in the entire series. A low specific gravity is, therefore, of considerable prognostic importance.

Phthalein Estimate.—A phthalein estimate was made for 11 patients. In 5 it was found to be from 40 to 73 per cent.; in 2, 30 to 40 per cent.; in 2, 29 and 22 per cent. respectively, and in 2, only a trace. The 2 latter patients died following operation. A normal phthalein as well as a normal specific gravity is present frequently with polycystic kidney and does not exclude the condition. A trace of phthalein return in two hours usually excludes a Rovsing operation and warrants nephrectomy only in exceptional conditions. The phthalein excretion and specific gravity were parallel with but few exceptions. In one case the specific gravity was 1020 and the phthalein 29 per cent. The phthalein test is of even more value, however, in differential functional estimates in determining which of the two kidneys has the greater functional capacity. It is of interest that a difference of several degrees in functional activity was usually noted between the two polycystic kidneys, even when other-

wise normal. This coincides with the comparative difference in size and functionating tissue usually found in the kidneys.

Microscopic Data.—In all but 10 of the 41 patients either red or white blood-cells were present in the urinary sediment. In several instances microscopic blood-cells were found when there was no history of gross hematuria. However, it is not true, as has been claimed, that red blood-cells are always present. The large number of cases in which there is a small amount of microscopic pus is noteworthy. This may be explained

Fig. 194.—The right pelvis is displaced downward and centrally. The outline of the true pelvis is irregularly oblong and the calyces largely obliterated.

as being due to infection from insufficient drainage from the calyces and pelvis as the result of cystic deformity. Casts were reported present in but 5 cases; they were described as hyaline and occurred only sparingly.

It is noteworthy that the ophthalmoscopic examination was negative in every case.

Tumor.—Renal tumor was noted in 31 of the 41 patients. In 3 patients the enlarged kidney was mistaken for tumor of the liver or gall-bladder. In 6 patients the condition was first discovered at operation performed for other abdominal conditions. It may be inferred, there-

'16—25

fore, that polycystic kidneys do not cause recognizable renal enlarge-
ment on either side. Renal tumor was described as bilateral in
but 18 of the 31 tumors palpated, showing that in a large percentage of
cases but one kidney is definitely determined to be enlarged on abdominal
palpation. Because of this, error in diagnosis is frequently made, the
inference being that the condition is unilateral. Particularly is this true
when there is a surgical complication in one kidney increasing its size
or directing the clinical examination to the affected kidney. It is obvious

Fig. 195.—The left pelvis is markedly compressed by multiple cysts so that only a narrow streak remains.
The calyces are obliterated and the true pelvis markedly flattened and elongated. Upper and lateral displace-
ment of the kidney is evident. The right pelvis shows abbreviation of the calyces and increase in the size of
the true pelvis, simulating a moderate degree of hydronephrosis.

that a diagnosis of unilateral polycystic kidney based on physical exami-
nation and without corroboratory data has no exact value.

Pyelography.—As might be expected, the cystic transformation of the
tissues about the renal pelvis has considerable influence on its outline.
There is recognizable deformity of the pelvic outline in more than 50
per cent. of polycystic kidneys (Figs. 194 and 195). The evidence of
abnormality is characterized by: (1) Flattening and obliteration of one
or more major calyces; (2) retraction and broadening of the various
major calyces; (3) elongation or rounding of the true pelvis; and (4)

displacement of the pelvis from its usual position and angle. The retraction of the calyces differs from that occurring with neoplasm in that they are broadened instead of narrowed, as in the latter condition (Figs. 196 and 197). Inflammatory dilatation is differentiated readily by the absence of pus in the urine as well as by the absence of clubbing in the calyx terminals. The possibility of retention of the injected medium because of imperfect urinary drainage which is frequent in polycystic kidney must be remembered. For this reason simultaneous bilateral pyelography should not be employed. Unnecessary ureteral cathe-

Fig. 196.—The calyces widely retracted and broadened throughout. Their outline is suggestive of pyonephrosis, but the absence of evidence of infection in the urine excludes inflammatory dilatation.

terization of the polycystic kidney is also to be guarded against because of the ease of infection resulting from the faulty drainage. As a precautionary measure the injection of a solution of silver nitrate is usually advisable before the ureteral catheter is withdrawn.

SURGICAL TREATMENT

1. *Nephrectomy (14 Cases).*—The various reasons for operation were: (a) Tumor with complete cystic degeneration and areas of necrosis in 4 cases; (b) lithiasis, unilateral, in 3 cases; (c) diffuse infection in 3

cases; (*d*) hematuria with complete cystic degeneration in 2 cases; (*e*) traumatic rupture in 1 case, and (*f*) hydronephrosis in 1 case.

One patient died as the direct result of the operation. Ten of the 13 patients were traced; all were alive except 1, who died of pelvic malig-nancy three years after the nephrectomy. Of the 9 living, 2 were oper-ated on one year, 2 two years, 2 three years, 2 four years, and 1 ten years ago. The good results following nephrectomy are remarkable and demon-strate very clearly that nephrectomy can be performed if the function of the remaining kidney warrants it. Nephrectomy was indicated in the

Fig. 197.—The major calyces are retracted and irregularly broadened at the apices. Some of the minor calyces are retained. This type might be confused with that caused by neoplasm but may be differentiated because of the bilateral deformity.

cases of hematuria because of marked cystic change and areas of tissue-necrosis. When there was infection, the process was so wide-spread that little secreting tissue remained and systemic toxemia resulted. In one case a moderate degree of infection was found in the other kidney as well, but not enough to interfere markedly with its function. Infection is evidently the result of incomplete urinary drainage resulting from the cystic change. The stones were multiple in two of the cases of lithiasis, and were scattered in various parts of the kidney. They were of the phosphatic type and probably secondary to imperfect urinary drainage.

2. Exploration for Unilateral Renal Lesion (5 Patients).—Before the value of the Rovsing operation was recognized two of these patients were only explored for unilateral tumor. In the cases of the others, either abdominal complication or evidence of renal insufficiency prevented further operation. One patient died two weeks later as the result of the exploration; two others died within two years after operation.

3. Polycystic Kidney Discovered on Surgical Exploration in the Course of Operation for Other Abdominal Diseases (8 Cases).—In this group the disease was in the latent stage and in 5 patients had given no clinical evidence of its existence. In 3 it was masked by other conditions in the abdomen and was overlooked clinically.

4. Rovsing Operation (10 Cases).—In 7 of the 10 patients the condition was recognized clinically prior to operation. Two patients died as the result of the operation, and 1, three years later. Of the remaining 7 reported alive, 4 were operated on during the past year, 1 two years ago, 1 three years ago, and 1 five years ago. Four of this number were operated on because of persistent hematuria. Recent recurrence of hematuria was noted in 1 patient operated on two years ago. Two patients were operated on with a view to improve the renal function, which was markedly reduced. One of them died three days later; the other was reported improved one year later. The remainder were operated on in the course of exploration for renal tumor.

As the result of operation the kidney becomes greatly reduced in size, but that it may subsequently increase in size was proved in a patient examined two years after operation. Therefore, punctured cysts may either regenerate, or others so small that they are disregarded at operation may increase in size, although as a rule not to the original extent.

5. Operation on Treatment for Other Lesions (4 Cases Found at Postmortem).—Three of these patients died at the hospital of surgical complications following operation for various abdominal complaints. The cystic disease was not advanced and was evidently in the latent stage, since there were no clinical data which might lead one to suspect polycystic kidney. One patient reached the Clinic in a semicomatose condition, dying several days later with uremic symptoms. The condition was discovered at necropsy.

6. Patients on Whom no Operation was Performed.—Twenty-one cases were observed in which there was a diagnosis of bilateral polycystic kidneys, but because the patients were not explored surgically and defi-

nite proof was lacking, they are not included in this report. Of this number, 11 showed such unmistakable evidence of marked renal insufficiency that operation was not believed advisable. The majority of the group represent the advanced stage of the disease, and the diagnostic data necessarily differed markedly from those regarded as surgical. The presence of bilateral cystic tumor, high blood-pressure, low specific gravity, and reduced phthalein return, together with a history of gastric disturbance and hematuria, hardly leaves the diagnosis in doubt.

In conclusion it may be stated that when renal function is reduced to the extent that the patient shows marked clinical evidence of chronic toxemia, when the blood-pressure is increased as high as 200 or more, when the various renal functional tests, such as absence of phthalein return or marked increase in blood urea, show marked renal disturbance, any operation is attended with considerable danger and is of questionable value. When, however, there is evidence of but a moderate degree of renal insufficiency, the Rovsing operation is often followed by considerable benefit. It is particularly indicated in the presence of larger cysts which frequently cause mechanical pressure on the adjacent tissues. The operation is also valuable in checking otherwise uncontrollable hematuria, but it does not always have a permanent influence.

Nephrectomy is indicated only in the presence of wide-spread infection, persistent hematuria, and destruction of renal tissue as the result of mechanical obstruction or lithiasis or other complication. It is, of course, possible only after the function of the remaining kidney has been demonstrated to be satisfactory. Functional tests are of particular value when the surgical kidney has caused marked systemic symptoms not easily differentiated from those caused by insufficiency in the remaining kidney. Whether or not the condition is unilateral in certain rare instances is not of great practical importance, since surgical treatment is feasible as long as the function of one kidney has been demonstrated to be good even if the kidney is polycystic. Whether or not a nephrectomy is permissible may usually be ascertained from the general clinical picture, cystoscopic examination, and the functional test of the opposite kidney.

THE REMOVAL OF STONES FROM THE KIDNEY*

WILLIAM J. MAYO

From January 1, 1898, to December 31, 1915, 450 patients with stone in the kidney were operated on in the Clinic (484 operations). Three died—a mortality of 0.6 per cent. This percentage represents the number of patients who died in the hospital without regard to cause of death or length of time after operation. The results achieved were due more to the painstaking care with which the diagnoses were made, the function of the kidney estimated, and the patients prepared for operation than to any purely technical feature of the procedures employed in removing the stones.

The presence of the stones was shown by the roentgenogram. By means of the pyelogram the urologist was able to say with certainty whether the stone was in the pelvis, calyx, or parenchyma of the kidney. On two occasions, previous to the use of the pyelogram, I exposed the right kidney on the basis of roentgenographic shadows only to find it free from disease, and the stones which had given rise to the shadows located in the gallbladder directly anterior to the kidney. It is true that these shadows can usually be identified as gall-stones by their concentric layers and density, but, as Carman points out, an occasional shadow may be confusing.

Stones in Both Kidneys.—Forty-eight patients (9.9 per cent.) had stones in both kidneys. A kidney containing small movable stones is more liable to exacerbations of infection, the result of temporary obstruction, than a kidney containing large stones. The large stones, because of their more or less fixed condition, may not interfere with drainage, and therefore may be the cause of comparatively few symptoms, even though the kidney is extensively damaged. Unless the condition in the opposite side is acute, our practice has been to remove the stone from the least involved kidney first, the second kidney being operated on after

the patient has recovered from the first operation, usually ten to fourteen days later.

Occasionally the second kidney has considerable function, even when it contains a large branched stone. The removal of such a stone may cause such severe lacerations to the already damaged kidney as to necessitate nephrectomy. On this account we have sometimes advised against operation on the second kidney unless symptoms necessitating it arise. Several patients of this description have gone for years without apparent progress of the disease.

In exactly half of our cases of stones in both kidneys the second kidney was found pyonephrotic, a condition necessitating nephrectomy.

Stones with Renal Anomaly.—In three instances stones were found in a single kidney and in two instances in a horseshoe kidney. The condition was diagnosed before operation as nephrolithiasis in an anomalous kidney. In two cases in which the renal condition had not been diagnosed considerable difficulty was encountered, not in removing the stone, but in determining the presence of a congenital single or horseshoe kidney. When the diagnosis had been made previously, the stone was readily removed from the affected portion. No complications followed in any case.

In one case of horseshoe kidney the stone had caused a pyonephrosis in the left half. This portion of the kidney was resected and recovery followed.

Renal stones were found in two patients with duplication of the renal pelves. In both the caudal pelvis was involved; in one, a pelviolithotomy sufficed, but in the other a resection of the upper half of the kidney was necessary.

Stones in the Remaining Kidney After Nephrectomy.—Stone formation or re-formation in the remaining kidney after nephrectomy is an uncommon occurrence. In our series there were only two known instances. I have been greatly impressed with the fact that some persons can maintain, not only life, but working power, with what amounts to not more than half a normal kidney. The following is an example:

CASE A44,090.—Male, traveling salesman, age forty-four years; had had stones removed from the right kidney and a nephrectomy of the left kidney for pyonephrosis four years before; was admitted to the hospital April, 1910, with stone in the remaining kidney. The patient was uremic and had edema of the lower extremities. The function of the kidney was so greatly impaired and the condition so serious that an

operation was not advised. However, the patient and his family realized the situation, and urged that the stone be removed; it was accordingly done, a large, soft stone being removed from a badly damaged kidney. The man made such a good recovery that he was able to go back to work. Two and one-half years later he returned with recurrence of stone, infection, and uremia. He was then operated on by C. H. Mayo, again made a good recovery, and was able to resume his work. Three years later he returned in a similar condition, and, although extremely uremic, rallied from the operation and returned to his occupation.

Recurrence.—Multiple stones in the parenchyma of the kidney are prone to recur. In one case in which I removed 28 stones from one kidney and 26 from the other I re-operated on the patient within two years for stones in both kidneys. Grave symptoms gradually developed each time the stones re-formed. It is possible that in the few cases of this type which have come under our observation the stone formations were secondary to hematogenous infections of the cortex. Fortunately, multiple parenchymatous stones in both kidneys occur but rarely; according to Braasch, they were found in but 5 of 48 cases of bilateral stones.

Persons having large and branched stones located in a hopelessly damaged and infected kidney are exceedingly liable to recurrence of stone following a conservative operation and, therefore, if the remaining kidney is sound, there is an increasing tendency on the part of surgeons to remove the affected organ at the primary operation. Previous to the nephrectomy urologic examination will have demonstrated the absence or the great reduction in functional capacity of the affected organ, and will have shown that it is infected beyond permanent restoration to even limited function. In our experience one of the most common causes of recurrence of stone has been attempts to conserve a badly damaged kidney which was of little use functionally and a continuous menace to the future health of the patient.

If both kidneys are involved extensively, it will, of course, be necessary to save them both. After the removal of the stones under these circumstances the pelvis of the kidney should be drained by a rubber tube through the cortex, and each calyx containing a stone, which has extended out into the parenchyma by atrophy necrosis until it can be felt with the finger as a softened area in the cortex, should also be drained separately through a counterpuncture. Drainage provides an opportunity for the relief of the infection and also for contraction of the large renal cavities from which the stones were removed. Drainage must be thorough and effected by means of a rubber tube and rubber tissue rather

than gauze. Gauze drainage tends to leave a fistula which is slow to heal. Small cigarette drains, however, are satisfactory for the drainage of the calyces and smaller stone-containing pockets, but a tube should be used for drainage of the pelvis.

Recurrence of stone is sometimes due also to attempts to remove the stone through a too small incision. In these attempts the stone is crushed or fragments are loosened from it which remain in the urinary tract to be painfully passed out later by way of the ureter or to become the nidus of a secondary kidney stone.

Another error to which Braasch has called attention is the fact that, in cases of multiple stones, roentgenograms may show only a single shadow, because the several stones are superimposed upon each other. We, therefore, should not trust entirely to the roentgenogram as to the number of stones present. We must produce all the stones that are shown and then introduce the finger into the pelvis and cavities to see that no others remain. On one occasion after a stone corresponding in location, size, and general appearance to the finding in the roentgenogram was removed from the pelvis, a second roentgenogram made before the patient was discharged from the Clinic showed a small stone which had remained hidden. To prevent these failures, a roentgenogram of the kidney is now made in every case of operation for the removal of stone before the patient is discharged from the Clinic. It has been stated that we cannot know whether or not stones have re-formed in a kidney unless this has been done. Unfortunately, however, unless a roentgenogram is taken immediately after the operation, we have no means of knowing whether stone shadows in a subsequent picture are those of stones that were overlooked or of new stones.

Our experience shows that the percentage of recurrence of stone will be small, certainly under 10 per cent., if at the primary operation good judgment is exercised in selecting and carrying out the best surgical procedure for each individual case.

Surgical Treatment

Hospital organization and operating-room technic have been so standardized that during an operation sepsis is rarely introduced from without. With good exposure the surgeon is able properly to handle septic renal conditions and prevent soiling of the operative field from within. Next to soiling from septic contents of the kidney itself, lack of proper hemostasis is the most frequent cause of those processes which

directly or indirectly, lead to sepsis and death, or those secondary conditions which end in recurrence of stone, hernia, or other sequelæ.

The incision outlined in Fig. 198, and which I have described previously, mobilizes the lower wall of the thorax, enables adequate ex-
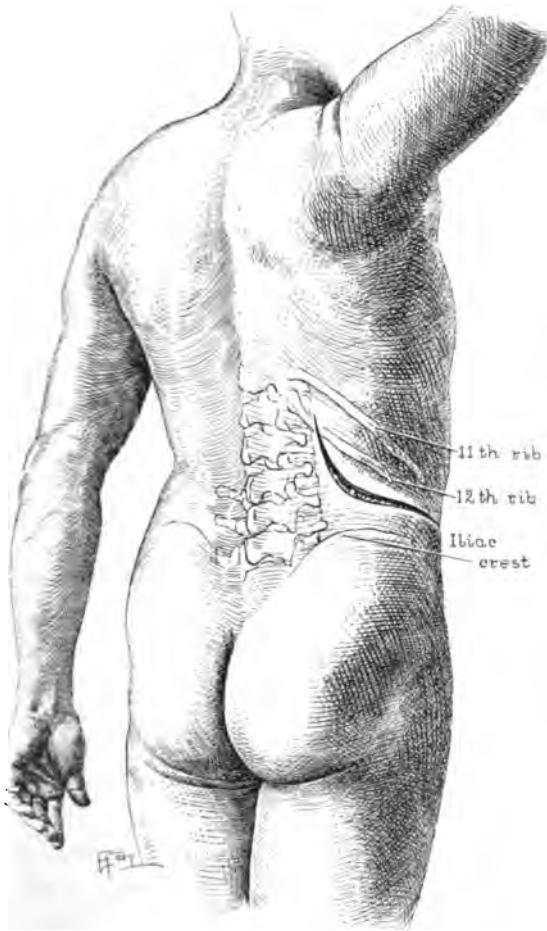
Fig. 198.—Proper incision for operations on the kidney.

posure of the kidney, and does not result in injury to important nerves or other structures. As pointed out by C. H. Mayo more than fifteen years ago, a cross cut of muscle, when properly sutured, is almost never followed by hernia. On the contrary, the muscle-fibers have little cohesion and are held together laterally by aponeurotic coverings

on which structures the protection against hernia in muscle-splitting operations rests.

Pelviolithotomy (206 Cases).—Pelviolithotomy is the most generally useful operation for stone in the kidney. As shown by Brödel, the anterior row of calyces and the anterior half of the posterior row in about 95 per cent. of the cases are supplied by the anterior renal arteries and the kidney is notched on the posterior surface. In the small remainder the contrary is true. The kidney is separated from its fatty capsule and brought well up into the wound, so as to expose the pelvis in the notch. If the stone is felt, it is removed by direct incision, and a search is made with the finger within the pelvis for others. The pelvis is then sutured with catgut, the kidney dropped back into position, carefully surrounded by its fatty covering (which should not have been lacerated in the separation), and two or three rolls of rubber tissue are introduced into the kidney space to provide temporary drainage. If the stone cannot be felt, needling or pummeling in an effort to confirm the *x*-ray diagnosis injures the kidney and serves no good purpose. The pelvis of the kidney should be exposed by dissecting the fatty tissues back from it in a flap-like manner, and the stone located and removed by the finger introduced through an incision into the pelvic cavity. The capsule should then be sutured with a few interrupted sutures of catgut, and the fatty fascial flap, to which I have previously called attention, placed and sutured in position (Fig. 199). The kidney should then be dropped back within the fatty capsule and the rubber-tissue drains introduced. Drainage of the pelvis of the kidney is rarely required after pelviolithotomy for uncomplicated stones in the pelvis. If necessary, it should be done not through the pelvis, but by counterpuncture through one of the calyces, preferably the posterior inferior calyx.

Combined Pelviolithotomy and Nephrolithotomy (34 Cases).—While usually it is possible to remove stones situated in the calyces through the renal pelvis, the communication between the renal pelvis and the calyx may be so small as to cause fragmentation of the stone in attempts at removal. Moreover, much cortical infection may be present about the stone, necessitating drainage. With the finger in the pelvis, a counterpuncture permitting easy removal of the stone should be made in the cortex above it and a drain inserted. Stones may be removed in this way from several or all the calyces. Each cavity should be drained separately; at least one tube should lead to the renal pelvis.

Nephrolithotomy (40 Cases).—Nephrolithotomy is an operation we seldom perform for uncomplicated stones in the pelvis and calyces. It

injures the kidney and is liable to be followed by secondary hemorrhage by way of the ureter, beginning four to ten days after operation. The hemorrhage may be so severe as to necessitate the removal of the kidney to check it. Several of our patients had hemorrhages after operation, and in four it was necessary to do nephrectomy to save their lives.
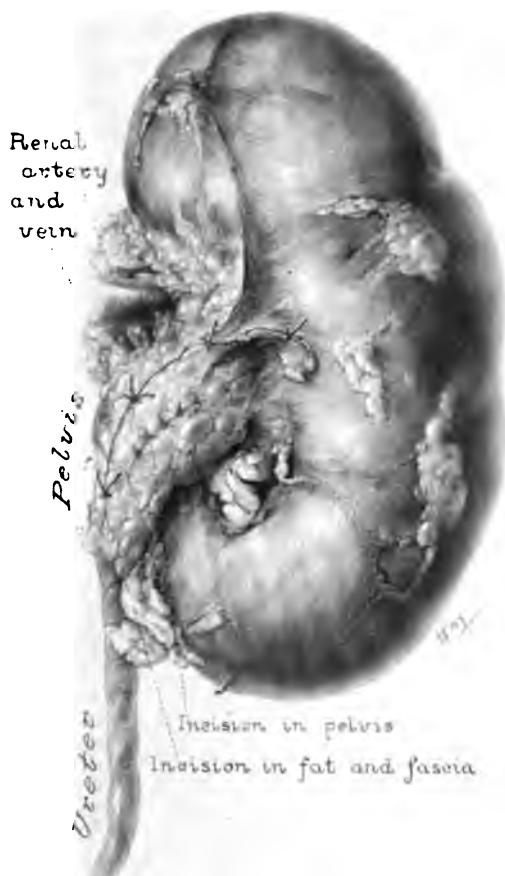
Fig. 199.—Pelvis of the kidney sutured. Fatty fascial flap replaced, following pelviolithotomy.

This, of course, is an extremely high percentage, and does not represent what might be called the normal incidence of secondary hemorrhage, since the stones were removed from the kidney through the cortex, not as an operation of choice, but only for good and sufficient reasons. It was done, for instance, in secondary operations when the kidney was firmly fixed as a result of former operation.

The rule is that if a stone is removed from an infected kidney by nephrolithotomy, a drain is introduced through the cut cortex of the kidney into the pelvis; otherwise drainage is unnecessary. If a number of stones are present and there is atrophy necrosis in various areas of the kidney-substance over the stones, it is wise to drain each cavity separately. Small cigarette drains are excellent for the purpose.

Nephrectomy (204 Cases).—In not a single instance in which nephrectomy was performed was there reason to regret the removal of the kidney either after examining the specimen or in the later events of the patient's history, while in a number of instances in which a conservative operation had been performed the necessity for secondary nephrectomy after some months or years of trouble made it evident that the excision of the kidney would have been the better primary operation.

In the larger number of cases in which nephrectomy was done there were pyonephrosis and stone, and nephrectomy was obviously the only treatment that could be considered. Four nephrectomies were performed following conservative operations for stone. In the small number remaining in which nephrectomy was done the function was so limited as to be negligible, but it would have been possible to save the remnant of the kidney. Should this have been done? Since stone did not form or re-form in the remaining kidney in any of these cases and no symptoms developed subsequently to indicate renal insufficiency, we must conclude that the practice followed was sound. In most cases nephrectomy is easily done through the incision described, but in some cases, especially of pyonephrosis, the kidney may be encapsulated by a massive wall of connective tissue and the attempt to remove it with the protective wall may cause the accidental opening of the pleura or more often of the peritoneal cavity. While neither of these accidents is of great moment (and I have never seen trouble follow if the pleural or peritoneal rents were promptly sutured with catgut), it is at least unnecessary. The most serious risk in the removal of such a kidney with its capsule lies in the fact that on the right side the vena cava or the duodenum may be injured during the operation.

In 1900, Dr. A. J. Ochsner and I saw Tuffier do a subcapsular nephrectomy. The opportunity to see this operation was alone worth the trip to France. In this country the mortality for nephrectomy in such conditions up to that time had not been far from 25 per cent. After exposing the kidney, Tuffier made an opening through the fibrous capsule down to the pyonephrotic sac and, with the hand, quickly decorticated the kidney. He then lifted it out from within the attached capsule

which turned back about the pedicle (Fig. 200), placed a pair of clamps across the pedicle, cut the kidney away, and packed the cavity with gauze. On my return I described this method, and I believe that subsequently subcapsular nephrectomy with the forceps treatment of the pedicle lowered the mortality of nephrectomy for pyonephrosis in America very materially. But the forceps method was clumsy and painful. It was possible, of course, by the use of catgut on a needle, to tie off the pedicle in sections and so avoid using the clamps, but if there had been

Fig. 200.—Subcapsular nephrectomy. Capsule incised along the superior border of the kidney and enucleation begun.

soiling of the field, there was danger that the needle and catgut passing through the pedicle might infect the vein. One patient in our series died from general septicemia which I believe had this origin.

In May, 1914, while on a visit to Petrograd, I saw that master surgeon, Federoff, make an addition to subcapsular nephrectomy which rendered the securing of the pedicle extremely easy. Drawing the kidney out of its capsule, with a knife he separated the capsule from the sinus of the kidney as it was folded back over the pedicle. This allowed

Fig. 201.—Subcapsular nephrectomy for pyonephrosis. Kidney drawn outside of the capsule. Incision being made which separates the capsule from the kidney sinus.

the kidney with the renal vessels to be drawn through the capsule, top and bottom, and made possible separate ligation of the vessels (Fig. 201).

The most difficult nephrectomies are those which must be done following a nephrotomy which has left a fistula leading to a remnant of
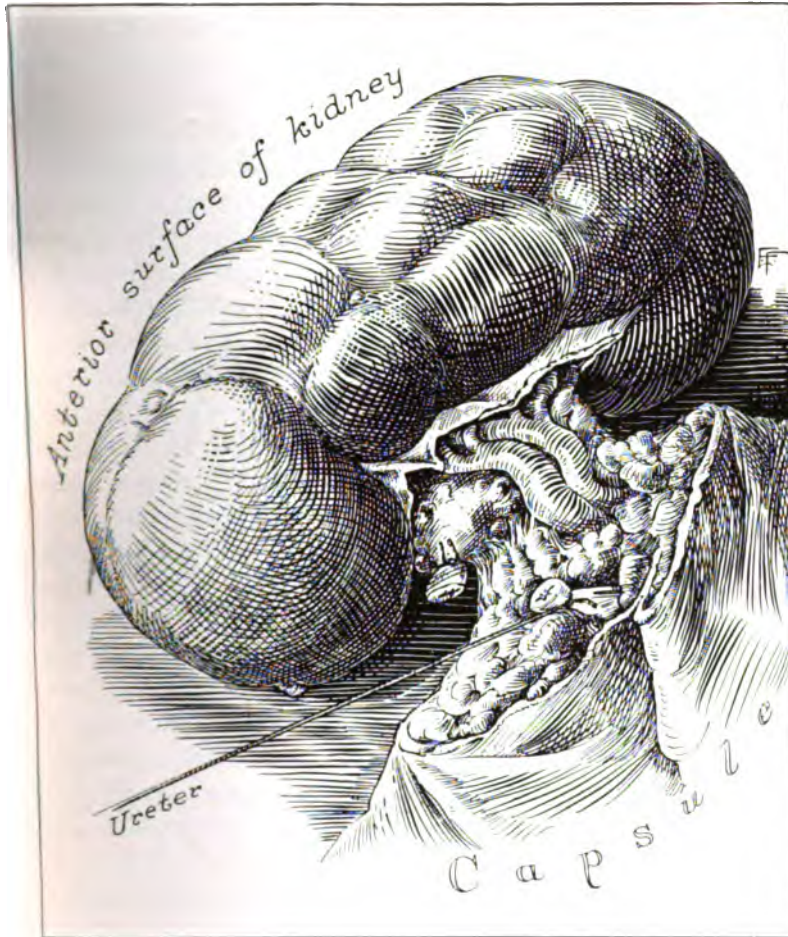
Fig. 202.—Subcapsular nephrectomy for pyonephrosis. Ureter tied and divided. Kidney drawn away from the capsule, exposing the renal vessels.

kidney. The safe way is to introduce a knife through the fistula to the kidney, and then split all the outer wall until a sufficient opening has been made for subcapsular nephrectomy (Fig. 202). If forceps are left on the pedicle, the admonition of Price should be remembered: Unclamp the forceps at the proper time—forty-eight to seventy-two hours—but

'16—26

do not remove them until from eight to twelve hours afterward in order that the tissues firmly compressed may have an opportunity to retract. Should the forceps be removed at once after unclamping, the ends of the vessels in their bite may be torn apart, permitting hemorrhage. In case there is a drainage-tube in a fistula leading to a calcareous pyonephrosis previously operated on, the drain should be removed several days before the nephrectomy, to reduce the local irritative infection.

COMPLICATIONS AND ACCIDENTS

Exploration.—In a small percentage of cases requiring operation it is impossible for the urologist to determine the exact condition of each kidney by means of cystoscopic data or functional tests. In such cases, therefore, exploration of each kidney becomes necessary. In this exploration, three methods may be employed: (1) Examination of the presumably sound kidney before operating on the kidney known to be affected; (2) exposing the affected kidney and judging from its condition the probable functional capacity of the remaining kidney; and (3) opening the peritoneal angle of the incision described and exploring the second kidney with the hand, intraperitoneally. The latter method is not of great value unless the kidney to be examined is grossly affected.

Intraperitoneal complications may be readily detected through the peritoneal incision. Exploration of the gallbladder, appendix, spleen, pelvis, etc., may be done easily and may yield information of great value.

Obesity.—In very fleshy persons, or occasionally those with crippling deformities, such as hip ankylosis, it may not be possible, with safety, to bring the kidney sufficiently into the wound to remove the stone. Sometimes fracture of the twelfth rib just behind the angle will give sufficient space. In other instances I have removed enough perirenal fat to expose the kidney *in situ*, much as one would expose the uterus within the peritoneal cavity.

Hemorrhage.—In performing an operation on the kidney large renal veins are occasionally injured, flooding the field with venous blood. I have checked this hemorrhage by using catgut on a small needle, and there has never been anything about the convalescence of the patient or the function of the kidney later to show that harm resulted. Injuries of the vena cava may be controlled in the same manner. Occasionally, however, renal arteries of considerable size have been injured. In one such instance there was a secondary hemorrhage and it was necessary to take the kidney out at the end of twelve days. I was astonished to see that the injury and ligation of this large branch of the

renal artery had resulted in acute degeneration of almost the entire kid-' ney. This is what we might expect from animal experimentation and would indicate that while conservation should be practised when veins are injured, primary nephrectomy may be a better procedure when there is injury to large arteries.

Laceration of the Pelvis of the Kidney.—In the attempt to explore the interior of the pelvis and calyx of the kidney with the finger the pelvis of the kidney may be considerably lacerated, but in our experience, if it is sutured with catgut and a fatty fascial flap is carefully applied about it, primary healing has always taken place. This is equally true in those cases in which the pelvis is badly lacerated in the removal of large stones. In a most difficult pelviolithotomy I once completely detached the pelvis from the kidney. It was re-attached with fine catgut sutures, which, in some situations at least, did not bring the separated fragment of the pelvis directly in contact with the part from which it had been torn. The suture line was covered with a fatty fascial flap and good union and function resulted.

Injuries to the Duodenum.—I have already described elsewhere injuries to the retroperitoneal duodenum. Such injury occurs on the right side, and usually is the result of the use of rat-toothed forceps in a hasty attempt to check hemorrhage from the pedicle of a kidney which has slipped. Rat-toothed forceps should never be used hastily in the control of hemorrhage in a situation where important organs may be injured, especially since it is so easy to control the hemorrhage by catching the vessels with the thumb and fingers. The artery fairly jumps into the fingers as the stream of blood leads the way to it, and a pair of mouse-toothed forceps may then be applied for temporary control. When injury to the duodenum does occur, the accident will show at the end of a few days, as necrosis permits escape of the duodenal contents. The patient thus injured will die within three weeks unless the abdomen is opened anteriorly, the retroperitoneal part of the duodenum exposed, and the fistula sutured.

REFERENCES

Braasch, W. F.: "Clinical Data of Nephrolithiasis," Surg., Gynec. and Obst., 1916, xxiv, 8–14.

Brödel (Kelly and Burnham): "Diseases of the Kidneys, Ureter, and Bladder," New York, Appleton, 1914, vol. i, p. 418.

Mayo, W. J.: "Accidental Injuries to the Descending Portion of the Duodenum During Removal of the Right Kidney," Jour. Amer. Med. Assoc., 1914, lxii, 343–345.

"Notes on a Visit to the Surgical Clinics of Germany and France," St. Paul Med. Jour., 1900, ii, 725–733.

"The Fatty Fascial Flap in Plastic and Other Operations on Pelvis of Kidney," Surg., Gynec. and Obst., 1910, x, 363–365.

"The Incision for Lumbar Exposure of the Kidney," Ann. Surg., 1912, lv, 63–65.

DIVERTICULA OF THE URINARY BLADDER*

GILBERT J. THOMAS

The frequent occurrence of diverticula of the bladder as observed in the urologic department of the Mayo Clinic has suggested a clinical study of the operative, non-operative, and postmortem cases since 1908.

Embryology.—A review of the literature and text-books of embryology as to the early development of the bladder is confusing. Many of the early writers are of the opinion that the anlage of the bladder is a differentiated portion of the allantois and is derived from this structure. Later writers, however, hold that the bladder is formed from the cloaca, a blind sac which is a dilated portion of the primitive gut, distal to the allantois. The cloacal membrane probably divides this sac into a ventral or large portion, which becomes the urogenital sinus, and a dorsal smaller portion, which becomes the rectum. Prentiss,[1] however, from his dissections thinks that a saddle-like partition between the primitive gut and allantois grows caudally and divides the cloaca into a dorsal rectum and a ventral primitive urogenital sinus. The partition thus made fuses with the cloacal membrane and divides it into the anal membrane of the gut and the urogenital membrane of the urogenital sinus. The mesonephric ducts which opened into the cloaca now open into this sinus. The buds forming the ureters spring from the mesonephric ducts near their insertion into the cloaca. As the urogenital sinus gradually becomes separated and differentiated from the rectum, certain absorptive changes take place in the proximal ends of the mesonephric ducts and primitive ureters. They become dilated, are taken up into the wall of the sinus, and as the absorption continues the ends of the ureters develop a separate opening and become separated from the ducts. The area between the ends of these two sets of ducts later becomes the point of division between a larger cephalic part of the sinus

or the anlage of the bladder and a smaller caudal portion, which becomes the urethra.

Etiology.—The etiology of these sacs from an embryologic standpoint can probably be explained as follows: The diverticula so frequently seen around the meati may be anomalies of mesonephric duct buds which normally form the ureters, etc., as Cabot and Binney pointed out from Huntington's case. Since portions of the Wolffian ducts are taken up into the bladder and form a portion of it, anomalies of development may occur along the trigone and floor of the urethra as far as the ejaculatory ducts. The mucosa of the bladder is largely endodermal in origin, except the trigone, which together with the floor of the urethra is mesodermal. The failure of the urachus to close may account for some of the sacs at the roof of the bladder. These observations indicate that anomalies of embryologic development may at least predispose to the formation of these diverticula since most of them occur where fusion takes place between the different embryonic tissues. The location of the openings is most often in the areas where anomalies may be expected. The rôle that obstruction plays in the formation of these anomalies is not clear, but clinically in a large percentage of cases it seems necessary for the development of symptoms.

Diverticula may be divided into two groups, congenital and acquired.

1. The congenital may be divided into: (*a*) Hour-glass bladder; the strangulation may be above or below the ureters; (*b*) double, split, or bifid bladder. In this type the separation reaches to the apex of the trigone and both cavities open into a common urethra, or a double urethra may be present.

2. The acquired type may be divided according to their etiology into: (*a*) Intra-uterine; (*b*) obstacles to urination (most frequent); and (*c*) traumatic.

The true congenital variety as observed clinically is a deformed bladder; *e. g.*, the hour-glass or the septum bladder, probably the result of maldevelopment. Obstruction or infection seems necessary to bring about symptoms in this group, although in the few instances observed in young people there was no obstruction nor was there a history of infection which might have caused a temporary obstruction. The walls separating the spaces in these deformed bladders are thick and contain all the coats of the bladder. Other genito-urinary malformations are usually found with this type, as bicornate uterus, double vagina, etc.

Some observers believe that the bladder in intra-uterine life is subjected to temporary obstruction which weakens certain areas of the wall without causing sacculation. During life these weakened areas quickly dilate or sacculate after obstruction is present. In this type there is congenital predisposition but an acquired etiology. The truly acquired variety is the many-pocketed bladder having demonstrable, long-standing obstruction with or without infection. The traumatic cases probably belong in this group and obstruction may or may not be an etiologic factor; the bladder after trauma to its coats may herniate into any cavity which offers little resistance.

Englisch[2] holds that all diverticula having a muscular coat are congenital, while those with a mucous coat only are acquired. In our cases the walls of the diverticula were not easily examined and we were unable to make a classification on this finding. Englisch further says that all diverticula are associated with some obstruction to outflow, either intra-uterine or during life. Ali Krogius,[3] quoting Pagenstecher, explains the latent development of symptoms on a mechanical basis and thinks the view of Englisch prejudiced. He says that the innervation of the diverticulum being the same as that of the bladder, the diverticulum has to work against the pressure of the full bladder when trying to empty itself. Because of this added work the musculature of the diverticulum hypertrophies. As long as the musculature remains adequate and does the work, there are no symptoms; when, however, the hypertrophy cannot go on, the urinary act is not complete and symptoms develop. Dilatation begins with possible displacement of the neck of the bladder from which obstruction of any grade may develop. Buerger[4] observed a case in which the contraction of the neck of the diverticulum was so great that a small cautery wire could not be passed into it. This was attempted because there was a papilloma within the diverticulum. At a previous examination the diverticular opening was easily seen and was of fair size. The muscle-tissue seemed well developed in the diverticular neck. Rokitansky[5] is of the opinion that diverticula are found only in bladders having hypertrophied walls, and that the mucosa is forced between the muscle-bundles; the opening is at first slit-like and then rounded. Interstitial changes in the muscle-bundles cause uneven resistance which invites sacculation. Chute[6] concludes that diverticula are formed from the pits which are situated on the outer side of the ureter and to this predisposing factor must be added increased pressure before a diverticulum is formed.

Cabot[7] calls attention to a case observed by Huntington, and reported by Binney, that showed a bud from the bladder which originated at the usual site of the left ureter. This was a case of congenital absence of kidney and ureter and the bud was found on the deficient side. Cabot is of the opinion from this case that diverticula probably originate from congenital buds which do not go on to ureter formation, but form the small sac which we know as a diverticulum. Cabot thinks that hernial protrusions in obstructive cases are not diverticula. He confines the word diverticulum to those pouches always of congenital origin occurring most frequently in certain localities of the bladder, but occasionally seen in almost any portion and not due to defective development or lack of closure of any recognized structure.

One of our cases may be similar to the one reported by Binney.

The patient came to the Clinic because of pyuria and pain in the right kidney-area. The patient did not speak English and a good history was not obtained. A functionless pyonephritic right kidney containing stones was diagnosed from roentgen and cystoscopic findings. About one-half inch anterior to the right orifice and toward the median line was another opening which could admit the end of the small finger. Upon observation apparent spurts of fairly clear urine could be seen, but these seemed to be synchronous with respiration. A catheter was passed with apparent ease and did not feel as if it coiled up. Argyrol was injected into the bladder and a cysto-ureterogram was made. This showed a sausage-shaped shadow extending from the bladder to the bony pelvis of the right side, where it was lost (Fig. 203). A shadow-casting catheter was passed into the right ureter, which was found in a normal position and did not empty into, or have any connection with, the anomalous cavity. This patient had had a pelvic operation in which trauma of the bladder may have occurred and which might have been the etiologic factor in producing the sac.

In the diagnosis of diverticulum of the bladder in patients having suggestive symptoms Garratt[8] makes it a practice to distend the bladder with an opaque medium. He believes that the diagnosis can be made easily by this means, and that it should be used routinely, because in many instances cystoscopic findings are not positive.

In operating on a case of hour-glass bladder Squier used two large clamps through the diverticulum opening, and by resection between the clamps and stitching up the cut edges a large bladder or sac was made. He does not recommend this operation in all cases, but thinks it applicable when the diverticulum is of the hour-glass type.

In Young's[9] case in which there was a papilloma he used a circular incision made from the vesical side surrounding the opening of the diverticulum.   By blunt dissection the surrounding tissues were dissected off and it was necessary to remove a piece of the peritoneum.   The peritoneum was closed through the vesical opening.   This method is

Fig. 203.—Small diverticula, probably congenital.

suggested by Young to remove diverticula and tumors which are situated on the posterior wall of the bladder and behind the ureteric openings.

Lower[10] suggested the introduction of a gauze strip into the sac to simulate a semi-solid tumor which makes its size easily seen and facilitates its removal.   Beer[11] suggests the introduction of catheters into the ureters before operation is begun, so that the ureters are easily found and constantly in view, especially where transplantation is to be done.

Lerche,[12] by means of a rubber bag attached to the end of a catheter and distended after introduction into the neck, both increases the size of the diverticulum and makes resection easy. Lerche reports the following routes for radical operation:

A. Vaginal.

B. Sacral.

C. Suprapubic intraperitoneal.

D. Suprapubic extraperitoneal.

The various simpler methods which are used are:

A. Incision through the vaginal wall and drainage.

B. Establishing of fistula by sewing to the skin.

C. Peritoneal drainage behind bladder.

D. Peritoneal drainage of bladder.

E. Forcible stretching of the orifice of diverticulum.

F. Curetment of mucous membrane of the diverticulum and suture of the latter without drainage.

G. Invagination of diverticulum and bladder, freshening of the margin of the orifice and closure intraperitoneally.

H. Enlargement of the orifice of communication between the diverticulum and the bladder or a new anastomosis.

I. Division of the walls of the bladder and diverticulum and suture of the cut walls.

J. Suprapubic drainage.

Englisch[2] reports 57 cases of diverticula up to 1904 in which there was perforation or rupture. He divides the cases that are most liable to perforation or rupture into four classes: (1) Chronic type with accumulation of pus and mucus; (2) acute suppurative; (3) ulcerating and gangrenous, and (4) perforating. In his opinion the location of the opening of the diverticulum in the bladder and its size are important factors entering into subsequent inflammation, perforation, etc.

In cases collected by Fischer there was a mortality in operative and non-operative cases of 66.7 per cent.; in operative cases, 40 per cent., and in non-operative, 84.3 per cent.

From January, 1908, to November, 1915, 27 cases of diverticulum of the bladder have been observed in the Mayo Clinic. Fourteen of these patients were operated on, 7 were not operated on, and 6 cases were found at autopsy. The average age of these patients was fifty-one plus years; the youngest, eighteen, and the oldest, seventy-three. The average age at onset of symptoms was forty-three plus years. Other

than these, numerous cases were observed which were regarded as false diverticula, probably the result of mechanical obstruction or inflammatory changes. These cases are not included in this report.

Previous Diseases.—Of these 27 patients, 6 (22 per cent.), gave a history of urethral infection and 2 (7 per cent.) had infection about the urethra associated with stricture. Five patients (18 per cent.) had had previous operations, two for prostatic obstruction, and three some operation on the bladder for drainage or exploration. Six (22 per cent.) had trauma of the bladder, suprapubic area, or of the perineum. The trauma to the perineum in two cases was the cause of obstruction which preceded the symptoms. The four remaining patients gave good histories of onset of symptoms immediately following the trauma of the bladder.

Urinary Symptoms.—Difficulty of urination was present in 19 instances (70 per cent.) and was noted in 11 (40 per cent.) as the first symptom. In 9 there was retention and catheterization had to be resorted to before urine could be passed. In 3 there was incontinence. Frequency was a first symptom in 9 (33 per cent.) and was the predominant symptom in 22. Hematuria was the first sign observed by the patient in 2 instances (7 per cent.), while macroscopic blood was observed at some time during the history in 8 (29 per cent.). We were able to obtain a history of repeated urination from one patient only, a symptom which has been frequently noted in published reports. In only two of our patients the symptoms began in childhood.

Clinical Data.—A suprapubic tumor was palpable in only 3 cases (11 per cent.); in none was a flank or rectal mass observed. In 11 cases (40 per cent.) a noticeable loss in weight was reported, and this seemed to be the most common clinical finding. In 6 (22 per cent.) the general loss of strength was graded as three on a scale of four.

Cystoscopic Data.—Cystoscopic examinations were made in 19 of our patients. In 16 (84 per cent.) there was a marked degree of cystitis. In 3 (15 per cent.) cancer was found in the bladder. In one case at postmortem a cancer was found in the diverticulum and was the cause of a perforation. Stones were found in the bladder in 4 (21 per cent.); in 1 they were found with a cancer. There were 3 cases with multiple small stones in the diverticulum. Urethral stricture was noted in 3 (15 per cent.) and was thought to be an etiologic factor in the production of the diverticula. In 8 (42 per cent.) the prostate was enlarged enough to cause obstruction to urination.

Location of Opening of Diverticulum.—The opening of the diverticu-
lum was found near the meatus in 6 of the 27 patients, on the right side in
2, and on the left in 4.   In 6 others the opening was found on the floor
of the bladder; in 2 near the urethra; in 4 on the posterior wall; in 2 in
the dome; in 3 the lateral walls were involved; in 1 an hour-glass con-
dition was found.   In the 3 remaining cases the opening was on the
posterior wall or base.   In 4 cases there were more than one diverticu-
lum.   In 13 cases generalized trabeculation of the bladder was present.

Roentgen-ray.—A cystogram was made in 16 cases, 10 showing posi-
tive findings.   In our opinion a routine cystogram in suspected cases in

Fig. 204.—Large diverticulum in the right wall of the bladder.   Shadow projecting on that of the bladder.

which there is difficulty of urination not otherwise diagnosed either with
or without the aid of the cystoscope will demonstrate a diverticulum in
a large percentage of cases.   Care must be taken in exposing the plates.
Many shadows of diverticula are missed when the radiogram is taken in
the ordinary anteroposterior position.   Exposures should be made with
the tube at different angles, so that the shadow of the sac is not super-
imposed on that of the bladder.   A coiled shadow-casting catheter or
bougie will definitely outline a sac when shadow-casting fluids cannot be
used.   Care must be taken in the introduction of catheters into these
sacs, and overdistention from injected fluids must be avoided because

perforation of the diverticulum might occur (Figs. 204, 205, 206, 207, and 208).

Urinalysis.—Pyuria was present in 17 cases and gross blood was noted in 3.
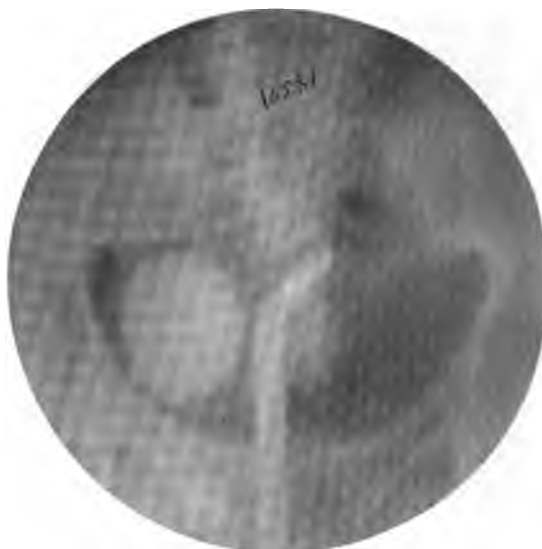
Fig. 205.—Shadow showing a diverticulum which had been carefully injected with argyrol through a ureteral catheter. Argyrol not allowed to pass into the bladder.
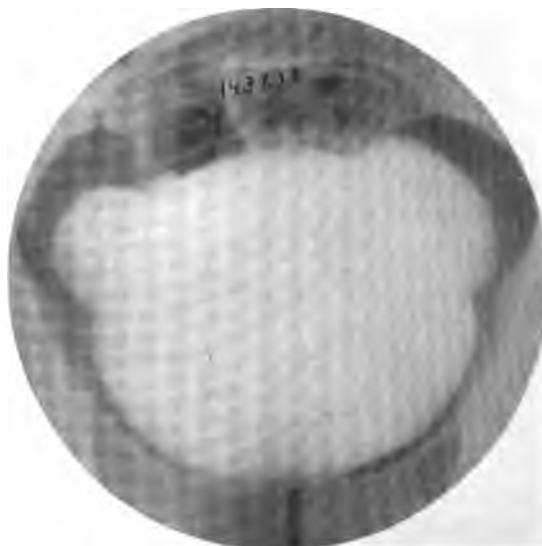
Fig. 206.—Multiple diverticula in the lateral walls of the bladder.

Medical Treatment.—Symptomatic treatment does not relieve patients of their symptoms and should be used only when surgical measures are contraindicated. Temporary relief is sometimes obtained, but recurrence is sure.

Fig. 207.—Multiple diverticula in the lateral walls of the bladder
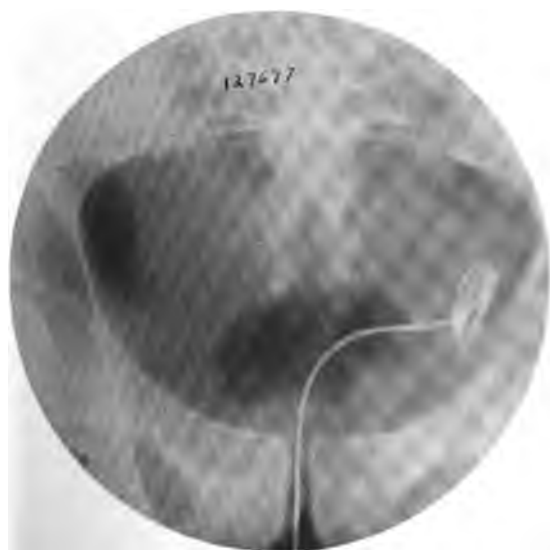
Fig 208.—Shadow-casting catheter carefully coiled in a diverticulum in the left lateral wall of the bladder.

Surgical Treatment.—In 14 cases some type of operation was performed. In 6 the diverticulum was resected. The extraperitoneal operation was done four times and the intraperitoneal two. A preliminary drainage was done in two cases preparatory to a resection. In 6 instances a drainage operation only was done or the diverticular opening was enlarged. In one case a septum was removed and in one a diverticulum was dissected loose and its opening enlarged so that the drainage was improved or complete.

Complications.—In three instances cancers were removed, one occurring with an hour-glass contracture of the bladder, the mass being in the upper chamber. Stones were removed from three patients, two having stones in the diverticula. It was necessary to remove the prostate in six instances. The prostates all proved to be benign. Dilatation of the ureter was found in one. In only one case was there evidence of perforation or of peritonitis.

This occurred in a man of seventy years who came to the Clinic complaining of a long-standing skin-trouble. For a number of years he had slight difficulty with urination and was quite sure that he was not emptying his bladder. He was in very poor physical condition, and a complete examination was not made. Urinary difficulty became so troublesome that he was confined to his bed. He had a sudden attack of pain in the lower abdomen, increase in temperature and pulse-rate, and collapse. He seemed to pass a fair amount of urine, and catheterization was not done for fear of precipitating an attack of uremia, which was the tentative diagnosis. He died in four or five days before a positive diagnosis had been made. At autopsy a moderate degree of hypertrophy of the prostate together with three diverticula were found. One of the diverticula had ruptured because of a cancer it contained. The diverticulum was situated along the posterior wall of the bladder.

Evidence of peridiverticulitis with resultant adhesions was present in every patient. The difficulty of removal in most instances made a careful examination of the diverticulum impossible. In three patients persistent postoperative fistula developed which did not heal for several months. Pyelonephritis was a complication in four; stone with pyonephrosis in one. In one instance only did the ureters open into the diverticula and the condition was bilateral.

Mortality.—In the six cases in which resections were done there were no deaths. One of these patients died some weeks after leaving the hospital, probably from acute renal infection. Two patients had drainage preparatory to resection; one of these died. One other had a carci-

noma in an hour-glass bladder and died after suprapubic drainage. In one case in which there were large stones in an enormously distended bladder with a diverticulum the patient died from the effects of suprapubic drainage. In six instances a diverticulum was discovered at autopsy; one of these patients had had a severe renal infection; one had had a few pus-cells in the urine; in the remaining cases there were no urinary findings. These patients did not have symptoms which could make a diagnosis of diverticulum probable, except the one with renal infection. In the cases complicated by carcinoma, stones, or severe renal infection the mortality is high.

Postmortem Findings.—A review of the postmortem findings shows some interesting facts. Marked pyelonephritis was found in 80 per cent. and was considered the major factor in causing death. A severe grade of nephritis was found in 78 per cent. In 55 per cent. there had been severe cystitis and in two patients the inflammation in the diverticulum was more marked than that in the bladder. Two patients died of pneumonia.

CONCLUSIONS

1. The embryology of the bladder is not clear, and in only a few cases does incomplete development account for the pathology. In some instances the condition may be congenital, but other factors seem necessary before symptoms develop.

2. In this group the average age of onset (forty-three plus years) would indicate that acquired factors (obstruction 86 per cent.) seem necessary for the development of diverticula clinically.

3. Trauma was a factor in 22 per cent.

4. The cystogram and leaded catheter are of great aid in diagnosis and may be the only positive findings.

5. Surgery is the best method of treatment. The choice of operation depends on the location and size of the diverticulum.

6. When resection is possible, the mortality is negative. In complicated cases the mortality is high because of renal and vesical infection.

REFERENCES

1. Prentiss, C. W.: A Laboratory Manual and Text-book of Embryology, Philadelphia, Saunders. 1915, pp. 213–214.
2. Englisch, J.: "Isolierte Entzündung der Blasendivertikel und Perforationsperitonitis," Arch. f. klin. Chir., 1904, lxxiii, 1–67.
3. Krogius, A.: "Contribution to Our Knowledge of the So-called Congenital Diverticula of the Urinary Bladder and Their Treatment," Urol. and Cutan. Rev., Tech. Suppl., 1913, i, 142–149.

4. Buerger, L.: "Congenital Diverticulum of the Bladder with a Contractile Sphincteric Orifice," Urol. and Cutan. Rev., 1913, xvii, 135.
5. Rokitansky, C.: A Manual of Pathological Anatomy, 1855, vol. iii, p. 48.
6. Chute, A. L.: "Two Cases of Diverticulum of the Bladder Treated by Operation," Boston Med. and Surg. Jour., 1912, clxvii, 316–320.
7. Cabot, H.: "Some Observations Upon Diverticula of the Bladder," Tr. Amer. Assoc. Genito-Urin. Surg., 1913, vii, 62–72.
8. Garratt, J. M.: "Diverticula of the Urinary Bladder, with Special Reference to Roentgen-ray Diagnosis," Surg., Gynec. and Obst., 1911, xiii, 292–294.
9. Young, H. H.: "Report of a Case of Vesical Diverticulum Containing a Cancer," Tr. Amer. Assoc. Genito-Urin. Surg., 1909, iv, 121–125.
10. Lower, W. E.: "An Improved Method of Removing a Diverticulum of the Urinary Bladder," Cleveland Med. Jour., 1913, xiii, 1–7.
11. Beer, E.: "Transperitoneal Resection of a Diverticulum of the Bladder," Ann. Surg., 1913, lviii, 634–638.
12. Lerche, W.: "The Surgical Treatment of Diverticula of the Urinary Bladder, with the Report of a Case and a New Device for Facilitating the Operation," Journal-Lancet, 1912, xxxii, 337–342.

TRANSPLANTATION OF THE URETER FOLLOW-
ING TRAUMATISM AND RESECTION OF THE
BLADDER FOR CANCER *

EDWARD STARR JUDD

Ureteral fistulas have occurred following traumatism and following operative procedure. Removal of the kidney to which the damaged ureter belongs has not been at all unusual in the past. And this procedure will continue to be the best method of treatment for those cases in which a considerable part of the ureter is involved, so that transplantation to the bladder cannot be performed. Before the kidney with the damaged ureter can be removed it must be demonstrated that the remaining kidney is functionally sufficient. The principal indications for ureterocystostomy have been threefold: (1) Injury to the ureter during hysterectomy, usually for advanced carcinoma of the cervix; (2) resection of the bladder for cancer located about the ureteral orifice; and (3) traumatism of the lower end of the ureter during difficult instrumental labor. Long[1] reports successful transplantation of both ureters following a hysterectomy for cancer of the cervix with involvement of the base of the bladder. He gives also the important features in the technic. Paton[2] reports successful transplantation of the ureter on account of traumatism which occurred during an operation for cancer of the cervix and resulted in ureterovaginal fistula. Torrance[3] reports a case of transplantation of the ureter from the vagina to the bladder twenty months after a Wertheim hysterectomy. He buried the ureter for some distance in a trough of bladder-wall. His case is especially important because he demonstrated that the ureter was patent and functionating two months after the operation. In a case of difficult labor at the Lying-in Hospital, New York, Markoe[4] transplanted the lower end of the ureter to the bladder and obtained a good result. Kelly and Burnam[5] state that ureterovaginal fistula following labor is not uncommon, though

they do not mention having operated on cases of this nature. Kelly reports one case of double ureterovaginal fistula in which, operating through a vaginal incision, he obtained a good result by turning both ureters into the bladder.

We have performed ureterocystostomy: (1) In two instances for ureterovaginal fistula following hysterectomy; (2) on two occasions for ureterovaginal fistula following labor, and (3) in 17 cases in conjunction with resection of the lower end of the ureter and a quadrant of the bladder for cancer.

CASE 1.—(102,891.) A woman, forty-one years of age, had had a hysterectomy performed elsewhere. The history showed that clamps had been left on and a gauze pack put into the vagina, and that urine had come into the vagina very soon after the clamps and pack were removed. Five months afterward we transplanted the ureter, which was dilated to about twice its normal size, showing that there had been some obstruction.

CASE 2.—(144,658.) A woman forty-two years of age, had had a very difficult abdominal hysterectomy performed in our clinic in February, 1916. In this instance the ureter had been apparently partly tied off, as we suspected, at the time of the hysterectomy, and a fistula had resulted. Shortly after the hysterectomy we made an effort to pass a catheter and found that the ureter was not patulous. At the time we operated to transplant the ureter we found it dilated to about twice normal size, and there was much scar tissue at the ureterovaginal juncture.

In both instances in which fistula followed hysterectomy the ureter was transplanted without much difficulty and the wound healed primarily. Cystoscopic examination made about three weeks after each operation showed that the ureters were open and that urine was coming into the bladder through them. Recent reports from these patients state that both have remained well. In one instance twenty months, and in the other eight months, have elapsed since the transplantation of the ureter.

The two cases in which ureterovaginal fistulas developed following labor were of especial interest to us because of the rarity of the condition. They are the only two cases of the kind that we have seen. In talking with Dr. Markoe, who has had a very large obstetric experience in the Lying-in Hospital of New York, he stated that his case, mentioned above, was the only one that he had seen.

CASE 3.—(130,856.) A woman, twenty-nine years of age, had gone through a very difficult labor three years previously. Six months after childbirth she had been operated on for vesicovaginal fistula and had obtained partial relief. Later she was again operated on by abdominal incision, but obtained no further relief. At the time she consulted us examination showed that she passed about half her urine in the normal way and had perfect control of it. In spite of this, however, her clothing was continually soiled by urine which leaked into the vagina. Cystoscopic examination did not reveal an artificial opening into the bladder, and ureteral catheters could be passed into both ureters without obstruction. However, with a vaginal speculum a small opening could be seen in the right side of the vagina, just above the base of the bladder, from which urine was draining. A catheter was put into the right ureter and the urine drained through it for a number of days. Meanwhile there was no evidence of leakage through the fistula. Since the opening was so small and it was found possible to control the urine by ureteral catheter, it was thought that freshening the edges of the fistula through the vagina and placing a few stitches across the opening would probably close the fistula. We attempted to do this and left a ureteral catheter in place for ten days. During this period there was no leakage, but just as soon as the catheter was removed the urine drained into the vagina, as it had previously. An abdominal extraperitoneal incision was then made. The ureter was freed down to the bladder and the lower segment tied off. The upper segment was transplanted into the bladder-wall. Since her labor the patient had had several attacks of what appeared to be pyelitis, accompanied by chills and fever. She had had pain in the region of the right kidney. Ten days after the ureter was transplanted she had a similar attack, and for a few days urine drained through the abdominal wound. However, at the end of four weeks her wound was entirely healed. Her temperature and pulse had been normal for some time. Cystoscopic examination showed that the ureter was functionating, although at times there was considerable pus in the urine which came down from the right kidney. I operated on this patient in August, 1915. In a recent letter she says that since the transplantation of the ureter she has had no further attacks of chills and fever and has remained entirely well.

CASE 4.—(143,263.) A woman, twenty-seven years of age, came with a ureterovaginal fistula complicated by a vesicovaginal fistula which had been operated on twice before we examined her. Although transplantation of the ureter, performed April 1, 1916, improved her condition considerably, the last time she was seen there was still slight leakage from the vesicovaginal fistula. At this time she was about three months pregnant. A few weeks ago we received a report from her in which she stated that leakage of urine had almost entirely ceased and her condition had improved.

In the 17 cases of cancer of the bladder very satisfactory results were obtained by transplantation of one or both ureters. Many of these patients were operated on for very extensive cancers of the bladder; some of them have since died of a recurrence. We have been able to trace other patients for several years, and during that time have examined them repeatedly with the cystoscope. In one instance, three years after the operation, the ureter was functionating very well. In a few cases, during cystoscopic examination, we observed that the urine flowed from the transplanted ureter into the bladder almost continuously, rather than by spurts, as under normal conditions. In other instances the urine seemed to enter the bladder normally. It is probable that the continuous flow of urine was the result of a chronically infected ureter in which peristaltic contractions could not take place because of the thickened walls. In none of the cases was there a permanent urinary fistula, though there may have been small amounts of leakage for short periods.

In every instance in which we have been able to make a cystoscopic examination at any time after the transplantation of a ureter we have found the ureter open. In a few cases it could not be catheterized, although the urine was coming through it into the bladder. It seems entirely probable that a stricture might form and close the ureter completely, but as far as we have been able to determine, this has not occurred in our cases except possibly in one case of cancer. However, in the case in which the ureter was practically ligated at the time the hysterectomy was performed very little urine had been coming down from the ureter for two weeks previous to the ureterocystotomy. We were in doubt as to whether there would be a great deal of function in the kidney, as the ureter had been ligated so long. A few weeks after transplantation of the ureter a functional test of the kidney was made. Although there was some function on the traumatized side, about five-sixths of the return was through the normal kidney. In this connection I may mention also two cases in which one ureter was deliberately ligated at the time of the operation for resection of a part of the bladder for cancer. The ureter was ligated because it was impossible to make it reach to the bladder, and since the operation had already been extensive, it did not seem advisable to transplant the ureter into the intestine. In both instances the ureter was considerably dilated and evidently had been obstructed by the growth for some time. The ureter was ligated with the idea of doing a nephrectomy later if advis-

able, but in neither case was nephrectomy necessary nor was any difficulty apparent from this procedure.   Both patients were operated on
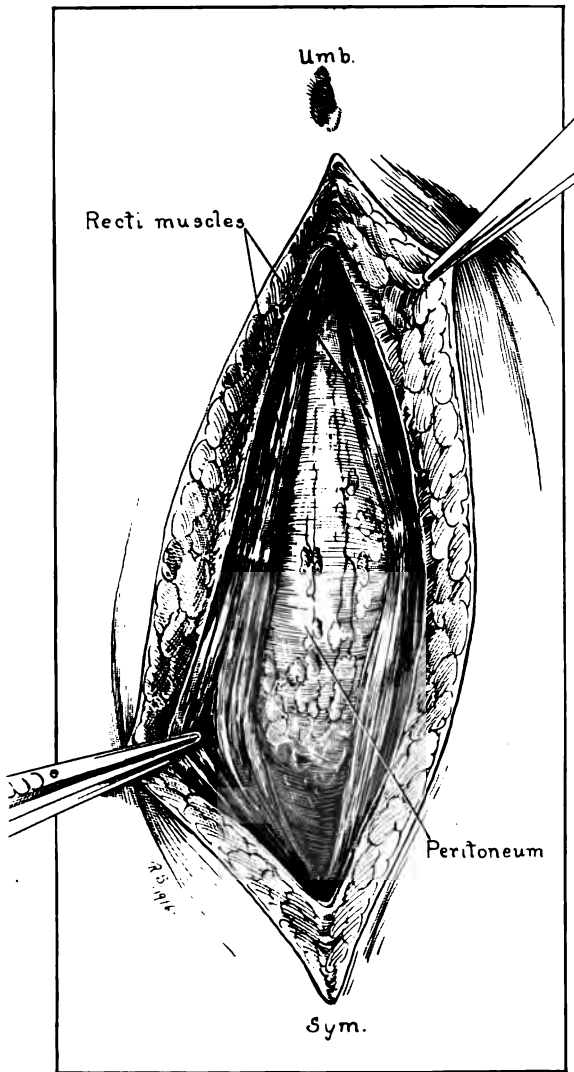
Fig. 209.—Regular suprapubic incision with recti muscles cut.   Bladder still in place.

more than a year ago and are alive at the present time.   One has a recurrence in the bladder, and a urinary fistula has developed from the bladder in the suprapubic wound, which remained closed for a number

of months after the operation.   In neither case have we been able to palpate the kidneys at any time.

<div align="center">TECHNIC</div>

The same technic was used in all the traumatic cases.   A straight rectus incision was made from the symphysis almost to the umbilicus (Fig. 209).   The peritoneum was dissected back and the ureter exposed (Fig. 210).   In one instance the peritoneum was opened.   The
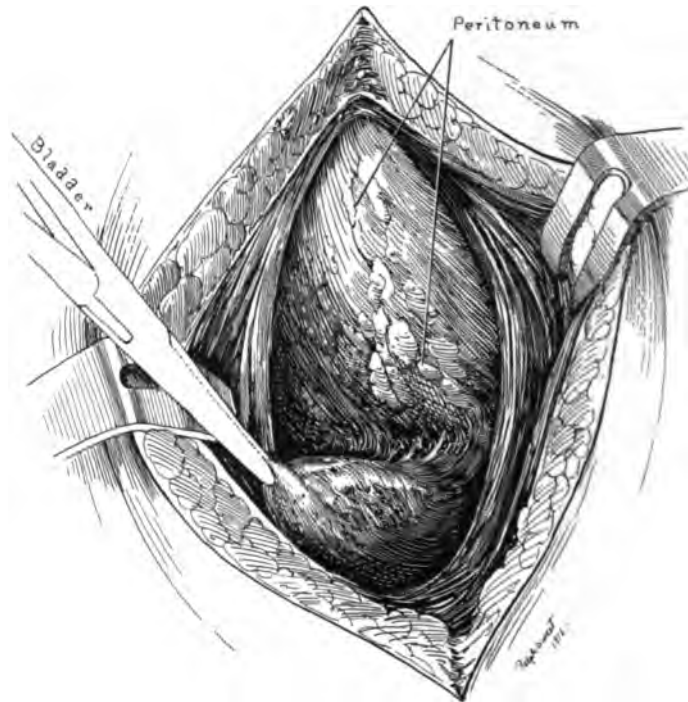
Fig. 210.—Peritoneum and fat dissected from top of bladder.

ureter was liberated as far down toward the bladder as possible.   In each instance there was considerable scar tissue and the dissection was continued into it (Fig. 211).   The ureter was divided between clamps and the lower end ligated with plain catgut.   The ureter was liberated from its bed sufficiently to make the anastomosis into the bladder free from tension.   In each instance the choice of the region in the bladder for transplantation depended on the amount of freedom from tension that could be obtained.   The end of the ureter was split for a short

distance and a small opening made into the bladder. We think it is essential that the end of the ureter should project into the bladder for a short distance. In order to hold it in place each of the two parts of the split ureter was stitched by a plain catgut suture to the mucosa of the bladder (Fig. 212). The coats of the bladder were then accurately stitched around the ureter. We endeavored to pass the
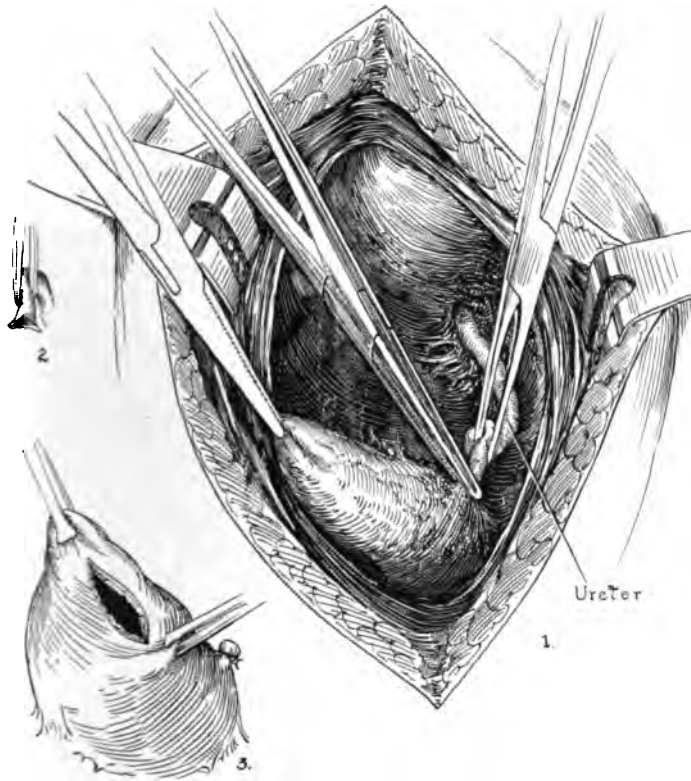
Fig. 211.—1, From four to six inches of ureter dissected out and clamped in place prior to cutting. 2, Cut end of ureter which is to be transplanted. 3, Bladder opened and ready for transplantation of ureter.

ureter obliquely through the muscle-walls of the bladder so that it would simulate the normal course. We never use anything but plain catgut for the sutures inside the bladder. Fine chromic catgut is used to stitch the ureter to the surrounding structures (Fig. 213). Usually there was a little soiling from urine during the operation, and in each instance a small drain was placed in the wound. In resections of the bladder for cancer the transperitoneal method suggested by C. H. Mayo

was employed. This technic is safer and more accurate for these cases because the peritoneum can be carried with the ureter, and the peritoneal covering of the bladder makes an accurate closure. In the cases in which the transperitoneal method was used the wound healed primarily and none of the patients had any urinary leakage.

Since 1908 we have performed intravesical transplantation of one

Fig. 212.—1, Interrupted suture placed on the ends of the transplanted ureter. 2, Starting to close bladder. 3, Bladder closed with ureter in place.
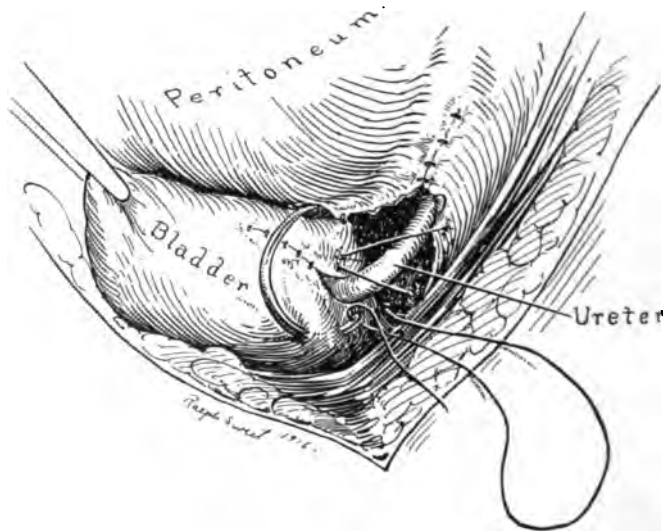
Fig. 213.—Drawing tissues around ureter and bladder to hold ureter in place.

of the ureters in 17 patients suffering from carcinoma of the bladder. Thirteen of these patients were males and 4 were females. The average age was between fifty-four and fifty-five years; the oldest patient was sixty-seven and the youngest thirty-three years of age. The average duration of symptoms was one and one-half years; the longest history was five years, and the shortest, two weeks. In each instance, with the

aid of the cystoscope, a clinical diagnosis of malignancy of the bladder was made; the surgical diagnosis was carcinoma, and the pathologist's report substantiated these opinions.

From one-third to two-thirds of the bladder was resected and the ureter transplanted into the remaining portion. Three of the 17 patients died in the hospital—an operative mortality of 18 per cent. One lived five days; one, six days; and one, twenty-three days. Necropsy showed that the patient who lived five days had an acute nephritis of the right kidney (left ureter had been transplanted) and left hydronephrosis. The second patient died on the sixth day from toxemia from extravasated urine. The third death, at twenty-three days, was due to an acute nephritis superimposed on the chronic condition. In this instance the right ureter had been transplanted and at necropsy it was found that it had been obstructed. There was a blood-clot in the ureter and in the pelvis of the right kidney. This patient also had a marked arteriosclerosis. Eight of the patients who survived the operation have since died. The average length of life was two years and one month. One patient lived seven years.

Patient 5756 lived three years and nine months after transplantation of the ureter. His physician wrote us that death was due to carcinoma of the stomach. This patient had returned to the Clinic nine months previously, at which time his general health was fair. His prostate was very hard and firm, his inguinal glands hard, and his legs swollen.

Patient 23,326 lived one year and five months. He gained in weight and strength for seven months following the operation, but died from recurrence.

Patient 24,745 lived seven years. He gained 40 pounds in the three years directly following the operation. His physician wrote that death was due to heart failure.

Patient 34,725 improved slightly but died in two months.

Patient 48,717 lived two years and one month. He returned for examination seven months after resection of the bladder and transplantation of the ureter. There was a recurrence of the carcinoma in the bladder, including the area into which the ureter had been transplanted. The transplanted ureter was not visible. The area was cauterized with a high-frequency current. The patient returned five months later, and the high frequency current was again applied. His last visit was eighteen months after the first operation, and at that time we explored the bladder but found the condition inoperable.

Patient 86,767 lived one year after the operation.   In the meantime his symptoms had returned.   One month before his death he came back to the Clinic and we operated for the recurrence in the bladder and for stones.   He died on the twelfth day following the operation.

Patient 92,613 lived six months after the operation.   For three months he gained in weight and strength.

Patient 99,860 lived five months after the operation.   At the time of the resection the carcinoma was broad-based and very extensive.   Half of the bladder was resected.   His general strength improved following the operation, but he died of a recurrence in the bladder.

We know that five of the remaining six patients are alive at the present time.   We have been unable to obtain a recent reply from the other patient, who was operated on in 1913, but when last heard from he was in good condition.   The following are short reports of the condition of patients still living:

Patient 42,568 wrote us six years after the operation that he was in good condition and had gained in weight.   One year and seven months after transplantation of the ureter we removed a stone from the bladder, and there was no evidence of recurrence of the malignancy.

Patient 69,825 had a third of the bladder resected for carcinoma, and the left ureter was transplanted.   He returned for an examination nine months after the operation, and a cystoscopic examination showed the transplanted ureter functionating normally—clear urine spurted from the left meatus and there was no evidence of a recurrence of the carcinoma in the bladder.   In a letter four years and one month after operation he states that his condition is good, that he urinates four or five times a day, and about once at night.   He has no pain and has not observed blood in his urine.

Patient 80,914 came to the Clinic with a broad flat carcinoma of the bladder extending to both ureteral orifices.   In August, 1913, the growth was excised and the right ureter transplanted.   This woman has returned several times for examinations.   Two years and five months after operation the cystoscope showed that the right ureter was functionating normally, but there was a recurring malignant caruncle.   This was removed with the clamp and cautery.   Nine months later (October, 1916) she returned in good condition.   Examination with the cystoscope showed that the right meatus was normal.   There was no evidence of recurrence of the carcinoma in either the bladder or the ureter.

Patient 86,191 had the right quadrant and floor of the bladder re-

sected and the right ureter transplanted for carcinoma. She has returned four times for examination. Her last visit was in November, 1916, three years and three months after operation. Her general condition was very good. She had had some frequency and burning on urination for the past six months. Cystoscopic examination showed that the transplanted ureter was functionating normally. However, the edges of the ureter appeared to be somewhat reddened and roughened. Otherwise it was normal, and no evidence of a carcinoma of the bladder could be found.

Patient 88,992 has not returned for examination, but wrote to us three years after his operation that he felt well. He says that he urinates three or four times during the day and night, has no pain, and has not observed any blood in the urine.

From this review of our cases we would conclude that transplantation of the ureter to another section of the bladder can be performed and the function of the kidney maintained. It seems that this is entirely feasible, that it is the procedure of choice in cases of ureteral fistula, and that it is much to be preferred to sacrificing the kidney.

REFERENCES

1. Long, J. W.: "Ureterocystostomy; An Improved Technic; Case of Double Ureteral Implantation into the Bladder," South. Med. Jour., 1910, iii, 171–175.
2. Paton, E. R.: "Transplantation of Ureter into the Bladder for Ureterovaginal Fistula," Brit. Med. Jour., 1907, i, 125–126.
3. Torrance, G.: "Successful Transplantation of Ureter From Vagina to Fundus of Bladder Twenty Months after Wertheim Operation in Which Greater Part of Trigone was Resected," Jour. Amer. Med. Assoc., 1912, lix, 1376–1377.
4. Markoe, J. W.: Personal communication.
5. Kelly, H. A., and Burnam, C. F.: Diseases of the Kidneys, Ureter and Bladder, New York, Appleton, 1914, vol. 2, pp. 354–355.

SOME OF THE PRINCIPLES INVOLVED IN THE TREATMENT OF PATIENTS SUFFERING FROM OBSTRUCTING ENLARGEMENT OF THE PROSTATE *

EDWARD STARR JUDD

The so-called adenomatous hypertrophy in the prostate which occurs in men past middle life has been shown by Tandler and Zuckerkandl to be a definite neoplasm or series of neoplasms held together by fibrous tissue. The process is very similar to that which occurs in the thyroid as multiple adenomas. The adenomas in the prostate compress the glandular and fibrous tissue into a definite, firm capsule; and it is the pressure of these tumors within the gland that gives rise to symptoms of obstruction. To relieve these symptoms the new-growths must be removed from the gland. Prostatectomy usually consists, not in the removal of the entire gland, but in the enucleation of the new-growths, the firm capsule being left intact.

Frequency of Occurrence.—According to most investigators adenomatous hypertrophy of the prostate occurs in about 60 per cent. of all men more than fifty years of age, though it is said only about 34 per cent. of these men have symptoms which require treatment. It is our custom to make routine examinations of all patients, and it has been of interest to review some of the records of examinations of the prostate. I have recently gone over the histories of 100 consecutive cases of men more than fifty years of age who were admitted to the Clinic with general complaints other than genito-urinary. The rectal examination showed a palpable enlargement of the prostate in every case. Sixty-five of these men were between the ages of fifty and sixty years, 14 between sixty-one and sixty-five, 9 between sixty-six and seventy, 7 between seventy-one and seventy-five, 5 between seventy-six and eighty. On a basis of 1, 2, 3, and 4, 44 had a relative enlargement of 1 (*i. e.*, though

slight it was easily recognized); 41, an enlargement of 2; 8, an enlargement of 2+; and 7, an enlargement of 3. In this series it was not possible to determine any definite relation between the enlargement and the age of the patient. The analysis of the urine in 59 of the 100 cases was negative; 36 showed pus; in 19 there was a history of Neisserian infection. It is probable that in some of these the enlargement of the gland was inflammatory. In 5 cases the urine contained casts. While none of these men came for treatment because of urinary symptoms, it will be noticed that a large percentage had some evidence of trouble from prostatic enlargement. Thirty-six had nocturia; 17 were obliged to get up on an average of once each night, and 19 two or more times each night. Forty-two had no evidence of trouble from the enlargement; 14 complained of some difficulty in starting the stream and of frequency in cold weather; a few complained of dribbling.

While this series of 100 cases is not large enough to be conclusive, it is suggestive. In our opinion this condition of the prostate is almost universal in men past

Fig. 214.—Suprapubic incision with bladder grasped by forceps preparatory to bladder incision.

fifty years of age. In some instances there were no symptoms with large lesions, but we know that most marked symptoms may be produced by comparatively small growths.

Symptoms and Diagnosis.—Usually the first symptoms produced by enlargement of the prostate are frequency of urination, irritability of the bladder, and slow stream often difficult to start. Occasionally there is acute retention of urine very soon after the first signs of trouble, but more often retention occurs after the ordinary symptoms of partial obstruction have existed for a long time. The process is almost always

gradual. Often frequency and irritability exist for some time before the person becomes aware that he is not completely emptying his bladder and it may be several years before the symptoms are severe enough to cause him to seek relief. Most of these patients have given a history of some obstruction for from two to ten years. The primary symptoms are produced by the growth in the gland. The secondary symptoms result from back-pressure of residual urine, which may cause changes in the bladder, ureters, and kidneys. Infection undoubtedly is an important factor in producing these secondary symptoms. Frequency and burning, the first indications of irritability of the bladder, are caused by the encroaching of the enlargement on the prostatic urethra and its extension into the bladder. If all patients could be operated on and the obstruction removed at the time of these primary symptoms and before any of the secondary changes take place, I believe the operation could be performed with practically no mortality and with an easy convalescence. With the gradual increase in the growth of the gland there is usually an increase in the amount of residual urine. The problem becomes serious when the amount reaches the point at which there is always eight to ten ounces in the bladder. The effect of residual urine has never been definitely shown, but there is no doubt that its complete and permanent removal is often very serious and sometimes fatal. It was this feature which years ago caused the high mortality following prostatectomy. In performing the operation on persons who for a number of months or years had had several ounces of residual urine, we removed the urine as well as the obstruction. Of course in the absence of obstruction the urine did not again accumulate and a large

Fig. 215.—Small incision in bladder.

number of these patients became uremic and died. We have long known that a patient who has been catheterizing himself for some time is a much better risk for prostatectomy than one who has not. It is hard to say just why patients become uremic on withdrawal of the residual urine. Necropsies on patients who have died under these cir-
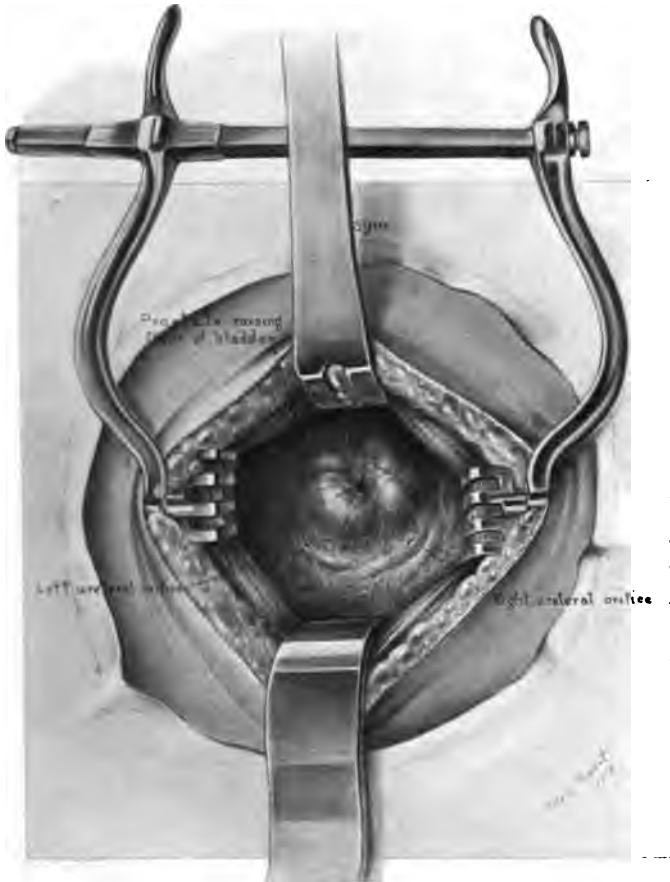
Fig. 216.—Self-retaining retractor in place and prostate raising floor of bladder with distortion of ureteral opening.

cumstances have almost invariably shown the cause of death to be an acute nephritis superimposed on the chronic condition. It would seem that the most feasible explanation of what takes place is this: During the time the obstructive process has been developing the amount of residual urine has been relatively increasing and there has been a backpressure into the bladder which sometimes dilates the ureters and ex-

tends up into the pelves of the kidneys. This pressure has increased so gradually that the patient has become accustomed to it. In some instances there are apparently no organisms in the urine though the infection probably exists in the tissues at the time. Removing the obstruction takes away all the back-pressure. In all probability this
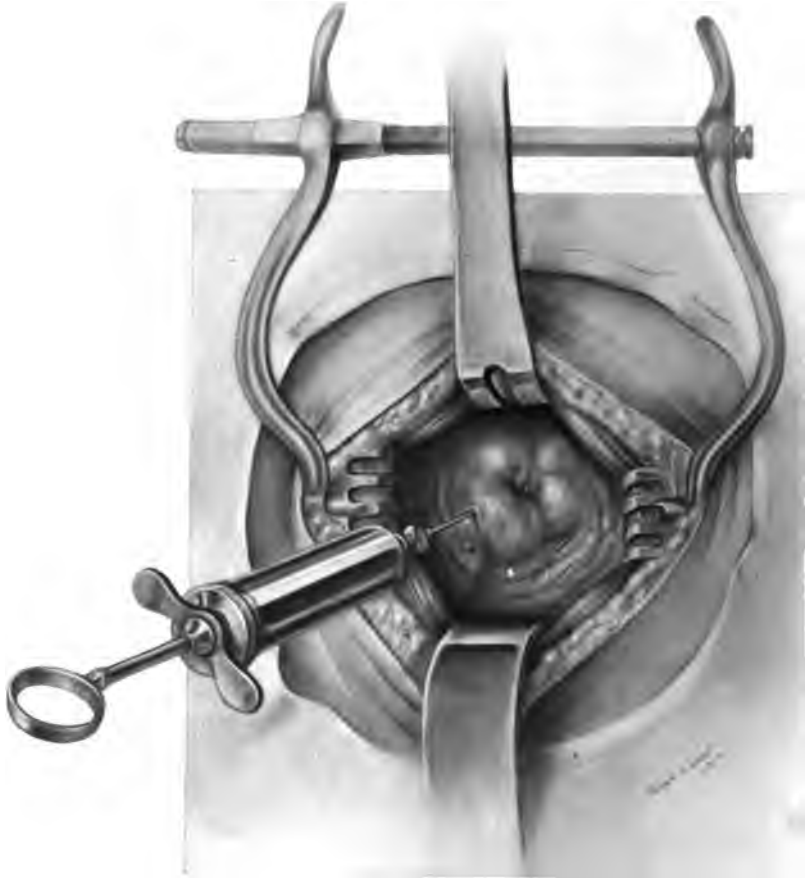
Fig. 217.—Injection of prostatic capsule and prostate with novocain and adrenalin, before removal.

would not be serious as far as the bladder and ureters are concerned, but in the pelves of the kidneys it makes almost a negative pressure so that the blood-vessels and the tissues of the kidneys which have been compressed in this way are now released and much more blood comes into the latter than was there formerly. In this manner congestion of the kidneys is produced, which, when severe, results in acute nephritis.

Another theory is that during the time the residual urine is in the bladder there may be some absorption from it into the general circulation. Accordingly, when the residual urine is withdrawn, absorption ceases. I have tried to counteract this effect by giving several urinary constituents to patients who showed symptoms of reaction after the withdrawal of the residual urine, but their condition was not relieved. This latter theory was suggested by the fact that often in the reaction following the removal of residual urine patients present many of the

Fig. 218.—In adherent prostates a uterine forceps may be used to aid in enucleation.

characteristics of morphin addicts who are denied morphin. While there is considerable question as to just what this reaction is, there is absolutely no doubt that it exists, and it is almost certain to occur when the residual urine is withdrawn.

Does it not seem that these facts definitely indicate that in any case in which there is enlargement of the prostate and a considerable amount of residual urine the treatment should be divided into two stages? In the first stage the residual urine should be withdrawn gradually and infection of the bladder cleared up as far as possible. The first stage of

'16—28

the treatment is always followed by some reaction.   Usually there will
be some general depression, loss of appetite, restlessness, and nervous-
ness.   The best index to the reaction is the specific gravity of the urine,
which is always much lower during this stage of depression.   Practically
every patient has a period of depression, and it is noteworthy that the
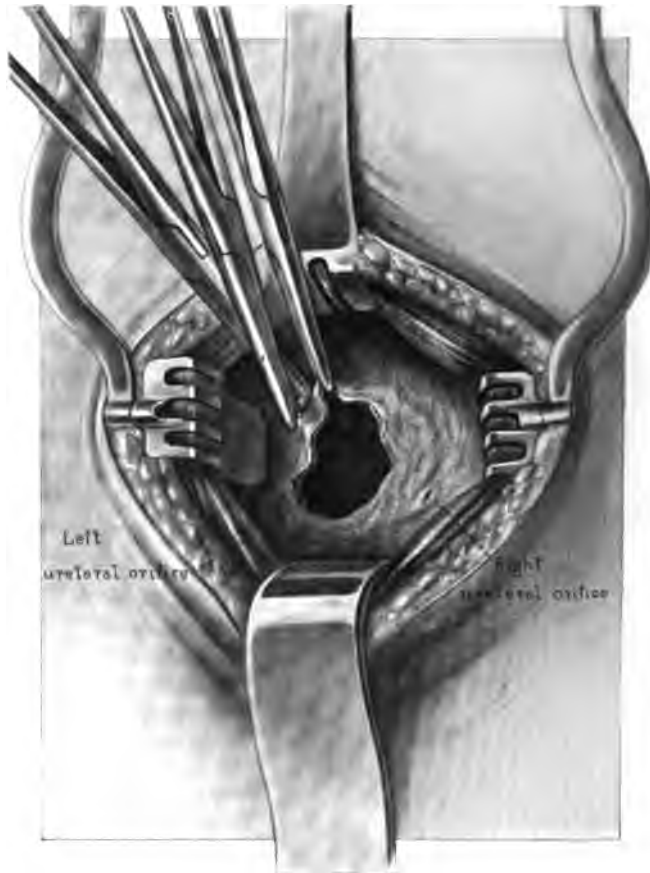
Fig. 219.—Cavity left after removal of prostate and bladder caught preparatory to suturing.

specific gravity of the urine and other findings correspond very closely
to his general condition.   In reviewing the preparatory stages of 50
prostatectomies, we found that the course was identical without excep-
tion.   In all there was a sudden drop in the specific gravity, accom-
panied by malaise, loss of appetite, vomiting, irritability, and sometimes
uremia.   This first stage usually lasts from three days to two weeks,

and is followed by a slow, gradual rise in the specific gravity and gradual improvement in the general health.   General irritability disappears and appetite returns.   The patient feels better than he has for years.   During the preparatory treatment there is always a fall in blood-pressure; it is not uncommon to see it come down 30 to 40 points in two or three weeks.
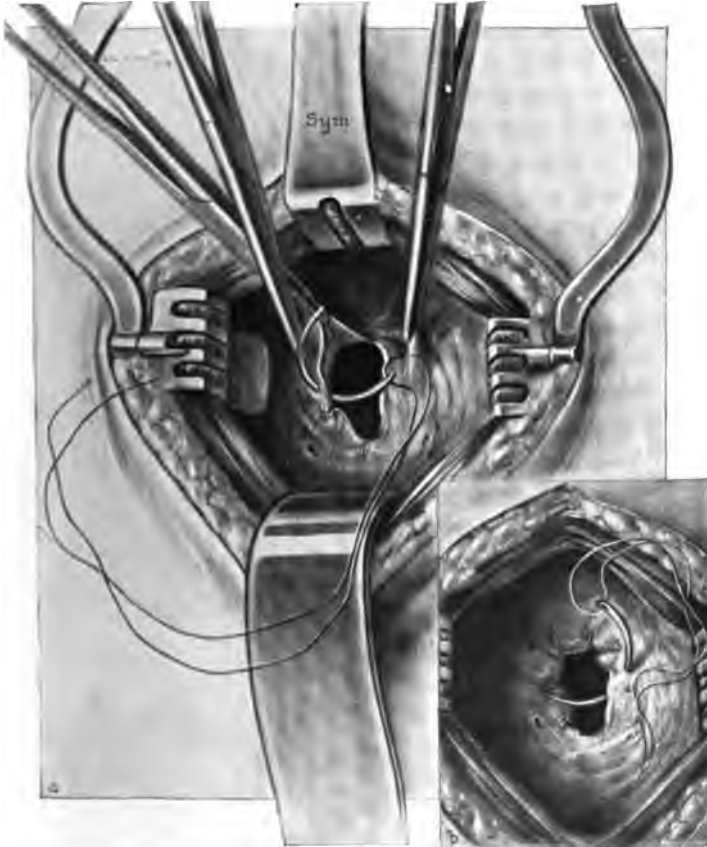
Fig. 220.—a, Prostatic capsule partially closed by interrupted suture; b, sutures in place investing mucous coat.

We prefer to prepare patients for prostatectomy by using a urethral catheter. If they have not previously used one and if there is no sign of a uremic tendency at the start, we begin by catheterizing two or three times in twenty-four hours.   If there is a uremic tendency at the beginning, the catheter should be used very cautiously.   When a patient becomes accustomed to the instrument, a soft permanent catheter

is fastened in by adhesive strips on the penis. With ordinary cleanliness and occasional change drainage may be continued in this manner for a number of weeks. In cases in which the catheter gives trouble, and in
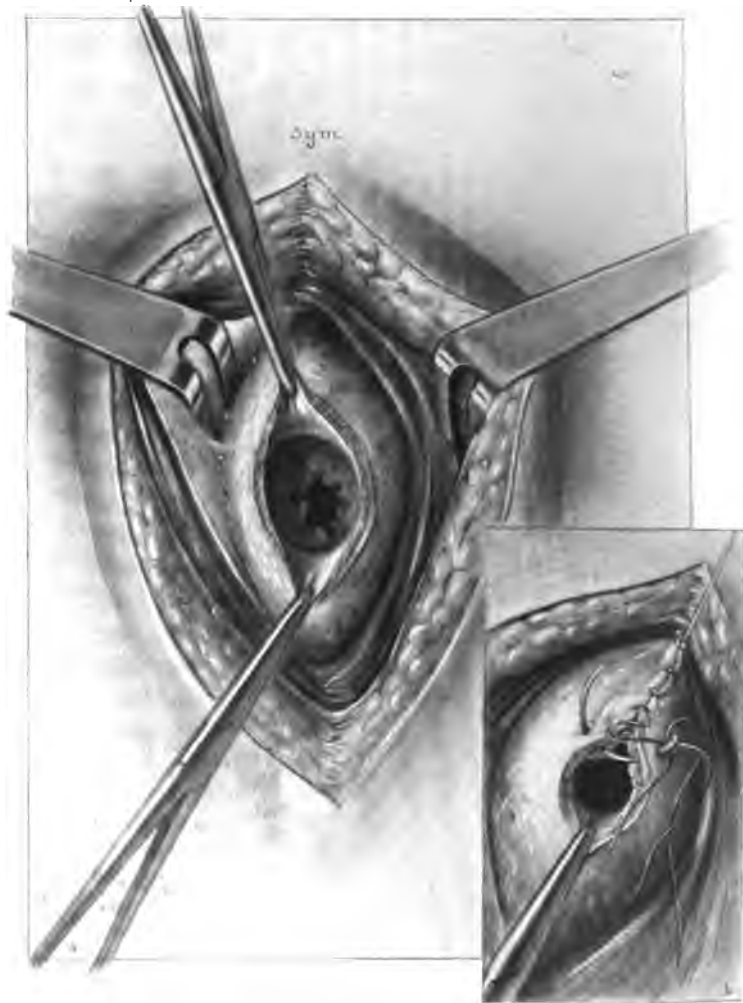
Fig. 221.—a, Self-retaining retractors removed and roof of bladder ready for closure; b, bladder closed with continuous suture of chromic catgut, avoiding mucous coat.

feeble, uremic patients with a large amount of retention, suprapubic drainage should be done. As soon as the reaction from the preparatory treatment has subsided, a prostatectomy may be performed with com-

parative safety. It is obvious that to operate without preparatory treatment brings the period of depression in the first few days after the operation—the time of greatest danger from the operative work.   If the

Fig. 222.—Closure of bladder incision completed with catheter placed at upper angle.

patient has weathered the period of depression beforehand, he has little or no reaction at the time of the second stage of the treatment, i. e., the removal of the enlargement.

The result of the examination of the first specimen of urine may be very deceiving, especially if the urine was passed in the office.   Very often the specific gravity is high and represents the patient's condition

as being much better than it really is. If he has been using a catheter the specific gravity ordinarily will not be so high. To illustrate—a specimen of urine passed in the office showed a specific gravity of 1025. The patient had 10 ounces of residual urine and had not used a catheter. Subsequently he was catheterized once a day for four or five days. At the end of that period a twenty-four-hour specimen showed a specific gravity of 1015, and the patient was feeling fairly well. He was then catheterized two or three times a day for four or five days and the

Fig. 223.—Complete closure of bladder with double row of catgut.

specific gravity dropped to 1009. In the meantime he had become restless, was not sleeping well, and did not care for much to eat. This reaction extended over a period of nearly a week, during which catheterization was done cautiously and with the idea of discontinuing it entirely should there be evidence of more severe reaction. At the end of seven days (two weeks from the beginning of treatment), however, the symptoms were subsiding, the patient's appetite was returning, and he rested better at night; the specific gravity of his urine had risen from 1009 to 1014. The reaction having subsided, it was possible to leave the catheter in the bladder almost continuously and to keep the bladder practi-

cally empty.   The patient continued to improve, and very soon he stated
that he was feeling better than he had in months past.   The specific
gravity of his urine never returned to what it was at the time of the first
examination (1025).   The high specific gravity at that time could
doubtless be explained by the possible concentration of the residual
urine.

This case illustrates the reaction that is observed in almost every one
of these patients while they are being rid of the residual urine.   We have
occasionally seen a patient who suffered no reaction in spite of the fact
that there was considerable residual urine; on the other hand, we have
seen patients with a small amount of residual urine who have had a very
severe reaction during this preparatory treatment.   Although it is
probable that infection plays a rather important part in causing the
reaction, we have been unable to demonstrate it.   Patients whose urine
shows no evidence of infection either at the beginning of, or at any time
during, the treatment frequently seem to be the ones who have the more
severe reaction.

The following table shows that in 50 cases the average specific grav-
ity at the first catheterization was 1016, while at the time of greatest
depression it was 1006.   Therefore, in the average case, it dropped ten
points from the beginning of preparation to the height of depression.
The figures indicate that the average specific gravity at the time of opera-
tion was 1011, a rise of five points from the time of greatest reaction.
In many instances the preparation was continued over a number of
weeks until all the evidence of reaction had disappeared.   In a very
few instances we observed a return of the specific gravity to what it was
at the time of the first catheterization in spite of considerable improve-
ment in the patient's general condition over what it had been four
months previously.

VARYING SPECIFIC GRAVITY AND BLOOD-PRESSURE DURING PREPARATORY TREATMENT: 50 CASES

	High	Low	Average
Specific gravity at first catheterization	1025	1006	1016
Specific gravity at greatest depression	1013	1001	1006
Specific gravity at operation	1021	1004	1011
Blood-pressure at first catheterization.......	230	140	166
Blood-pressure at operation................	190	110	145
Functional test at operation...............	60%	12½%	40%

The change in the blood-pressure during the period of preparation
would seem also to indicate a change in renal function during this period.

Apparently patients with a high systolic pressure will stand operation well, but if the diastolic pressure is high, especially if it is out of proportion to the systolic, their chance of withstanding surgical procedure is not nearly so good. The average systolic pressure in these 50 cases was 166; during preparatory treatment this average dropped 21 points, so that it was only 145. A part of this change may be attributed possibly to the loss of appetite and lessened activity. However, in spite of the fact that the patients returned to a normal diet and free exercise the blood-pressure did not return to its former high point.

The phenolsulphonephthalein test of the function of the kidney averaged 40 per cent., which, in our experience, is a safe limit in these cases. The highest functional result was 60 per cent. and the lowest, 12.5 per cent. Of course the risk would be great in operating on a patient whose return was only 12.5 per cent., unless everything else was favorable. The functional test is very important in determining the operability. However, it must be borne in mind that an infected kidney may show a high return, and for that reason a good output does not necessarily mean a safe operation, though a low test would indicate considerable risk in operating.

Data in regard to the specific gravity of the urine of 25 patients under preparation showed that at the beginning of their treatment the average specific gravity was 1015. After eight or nine days of preparation it dropped to 1004, and although preparation was continued for nine weeks, it never again became more than 1009. At this point, however, the patients were considered good risks for prostatectomy.

In conclusion I would state that preparatory treatment is of the greatest importance in all bladder and prostate cases. Preparation should be accomplished by urethral catheterization as far as possible. If this procedure does not accomplish the desired results, it will be necessary to institute suprapubic drainage and then wait until the reaction subsides before attempting prostatectomy. Sometimes it has seemed that the reaction subsided a little more quickly with suprapubic drainage than with urethral catheterization. However, suprapubic drainage has the added danger of infection and very severe reaction. The two-stage treatment described will considerably reduce the mortality.

POSTOPERATIVE COMPLICATIONS FOLLOWING PROSTATECTOMY *

JOHN L. CRENSHAW

While success in prostatectomy cases is dependent mainly on careful preoperative selection and preoperative preparation, many patients who would otherwise recover will die if postoperative care is neglected. Moreover, much can certainly be done after operation to add to the patient's comfort and hasten his convalescence.

In the past few years at the Mayo Clinic the various operative modifications of suprapubic prostatectomy and subsequent drainage, as well as many variations of postoperative treatment, have been tried out, and either continued or discarded according to their efficacy. After many changes in methods our present and satisfactory technic is briefly as follows:

1. A relatively large incision over a comparatively empty bladder, extraperitoneal, if possible.

2. Rupturing the prostatic capsule by inserting a finger into the urethra, sweeping the gland free from its capsule and delivering it into the bladder, at the same time tearing it from the mucosa of the prostatic urethra. If the capsule bleeds freely, bleeding tags are controlled by continuous catgut sutures or rarely by a long gauze pack brought out through the wound. The wound is closed with the usual catgut and interrupted silkworm sutures with a No. 32 French, soft, pure rubber double-eyed catheter in the upper angle and a small split or half rubber tube in the space of Retzius and out through the lower angle of the wound. The bladder tube is tied with the loose ends of the upper silkworm suture after the skin knot has been tied, so that when the suture is cut to remove the tube, the skin stitch is not disturbed. The tube in the space of Retzius is not sutured, but has a large safety-pin in its free

end to prevent motion. Ether anesthesia by drop method is used. The operation usually takes from ten to fifteen minutes, its brevity avoiding any ether complications.

When taken from the operating room, the patient is put into a warm bed with hot bottles around him, and rectal saline is started. The bladder is irrigated only sufficiently to keep the tube draining, clots being washed out with a two-ounce syringe; the size of the syringe avoids overdistention of the bladder. As far as possible, opiates are withheld, though a single dose of morphin and atropin is usually given the first night. Water by mouth is encouraged as soon as the patient awakens from the anesthetic, and light diet is started the morning after the operation, with a generous tray after the fifth day if desired. It is our usual practice to get the patient up on the third day, and earlier if indicated. Cardiac or other complications necessitate a longer stay in bed. One ounce of Epsom salt is given on the third morning. Dressings are changed as necessary. Tubes are undisturbed until the fifth or sixth day, by which time there is a more or less permanent canal formed around the rubber drain which prevents somewhat the spread of urine and infection to the rest of the wound. It is to be remembered, however, that following the drainage of a distended bladder the bladder in contracting often causes a tube which was in the proper position at the time of operation to prod into its base later. A continuation of spasms of the bladder after the urine is comparatively free from clots indicates the withdrawal of the tube for an inch. This generally gives immediate relief.

On the fifth day the tube in the space of Retzius is replaced by a narrow wick of gauze with a safety-pin attached. The bladder tube is replaced on the sixth day by a smaller male catheter which is held in place by a piece of enameled fishline. The ends of the fishline are fastened to the skin with adhesive on opposite sides of the incision, so that contact with the wound is avoided and the changing of dressings is facilitated. Enameled silk fishline has the advantage of other suture material in that it does not stretch and is non-absorbent. The gauze in the space of Retzius is changed daily and shortened with each change until it is finally pushed out. The bladder drain is replaced by successively smaller catheters as the wound closes. Eventually the catheter is clamped off for twenty-four hours and removed. A small, soft catheter may be placed in the urethra about the third week if necessary, either partially or continuously, according to how the patient voids and whether

or not he has used a catheter before the operation. With better postoperative technic, the necessity for the use of permanent catheters in the urethra is being avoided. The silkworm sutures are removed not earlier than the fourteenth day.

Most wounds in the bladder will close of their own accord if kept free from collections and reasonably clean. A previous suprapubic sinus in the midline should be excised at the second operation. The preparatory stab drain should be made an inch to one side of the midline. It will usually close by the time the midline drain of the subsequent operation is ready to be removed. Every effort should be made to stop any urinary drainage from the lower angle of the wound where the drain has been placed in the space of Retzius, and to get this part completely healed before removing the tube from the upper angle. It has been our experience that in almost every instance of a slowly closing wound the leakage has been from the lower angle. Keeping the skin wound open at the points of drainage and using a sharp curet or caustic about the end of the second week, in addition to keeping the bladder empty by frequent voiding or catheterization, will usually secure an early closure. Cystoscopy should always be performed in cases in which a sinus persists; obstructing tags should be removed, and the possibility of a lost sponge should be kept in mind. Occasionally a plastic closure will be necessary. When it is not advisable to use a catheter in the urethra, a modified colostomy pad or bottle is often useful until the suprapubic wound closes. The use of zinc oxid and other ointments on the wound should be avoided, as they become infected and cannot then be completely removed.

Patients are encouraged to drink water, milk, and buttermilk in abundance. If the appetite is poor, a little beer may be given. As soon as the stomach is settled, 15 grains each of hexamethylenamin and acid sodium phosphate in solution is given every three hours. Hot packs, subcutaneous, intravenous, or rectal salines are used freely when indicated.

COMPLICATIONS

In considering postoperative complications, I have confined myself to the more common types, and have not taken into account the numerous terminal infections and complications of fatal cases which bear no relation to the usual postoperative treatment. The patients who have been considered in this review have had the most careful preoperative

examination and preoperative preparation, so that many of the usual complications have been reduced or eliminated.

Postoperative complications may be divided into two groups; namely, infectious and non-infectious. In the first group may be included wound infection, pyelonephritis, epididymitis, phlebitis, cystitis, etc. In the second group are hemorrhage, cardiac disease, acute renal suppression, embolus, apoplexy, etc. Many of the second group, however, may be due indirectly, at least, to infection.

The prevention of infectious complications must be initiated through preparation before prostatectomy; that is to say, by thorough drainage of the bladder and the establishment of immunity against the usual urinary pathogenic organisms. This can be accomplished by improving the general health and increasing the elimination, thus increasing the resistance to infection. When there is marked cystitis, the bladder should be cleared up before prostatectomy. If stones are present, they should be removed.

Wound Infection.—In speaking of wound infection, I refer not to the mild infection which follows any open wound, but to the foul, sloughing infection which may play a major rôle in the causation of such complications as epididymitis, cystitis, pyelonephritis, phlebitis, etc. Care should be taken that at the time of operation the bladder is as clean and as nearly empty as possible, in order that contamination of the wound may be avoided. Sutures should be tied relatively loosely, and the edges of the skin should be carefully approximated without inversion or eversion. Continuous skin sutures of horsehair, catgut, etc., have usually been followed by more infection than interrupted silkworm sutures. Leaving all drains undisturbed until the fifth day unquestionably walls off the drainage and reduces the infection. With the first evidence of redness, swelling, or pain in the wound, usually about the third or fourth day, a continuous hot potassium permanganate dressing is applied. The rapidity with which the odor and other evidences of infection disappear after such treatment is astonishing.

Pyelonephritis.—This, probably the most frequent complication, often exists before operation in its various degrees either as the result of vesical retention or antedating any disturbances of the bladder. Serious destruction in one or both kidneys can often be overlooked in the presence of a very large prostate and a purulent bladder, and discovered only at postmortem. When it has not been advisable to perform cystoscopy on the patient, or when the ureters were not located

by the cystoscope, a cysto-ureteropyelogram should be made, the bladder having been filled with an opaque medium and the patient placed in the Trendelenburg position for ten minutes, and a roentgeno-gram taken in that position. This sometimes gives a definite idea as to the amount of destruction in one or both kidneys. If the technic is properly carried out, an absence of the medium in the ureter usually means a normally contracted vesico-ureteral valve and an absence of any marked degree of infection. In the presence of infection, the valve is relaxed and the ureter atonic, allowing the free flow of the bladder medium to the ureter and the pelvis of the kidney. All degrees of dila-tation are exhibited, from that of slight distention to that of an extremely dilated sacculated ureter and pyonephrotic kidney.

Acute pyelonephritis may occur at any time from the day of the operation to several weeks thereafter. The symptoms are usually characteristic—several days of increasing fever and malaise, possibly with pain in the back, followed on consecutive days by severe chills, increased temperature, and sweats, and then a gradual subsidence of all symptoms. Attacks usually last from three days to a week and tend to recur. Prophylactic treatment consists of: (1) Avoiding septic collections in the wound and bladder; (2) forcing fluids, and (3) administering 15 grains each of hexamethylenamin and acid sodium phos-phate in solution every four hours from the third day after operation. During an attack the patient should be kept quiet, though not necessarily in bed. Liquid diet, saline laxatives, and acetylsalicylic acid (aspirin) if necessary to control the pain, should be given. The symptoms are often alarmingly severe, but in acute attacks the prognosis may be excellent.

Epididymitis.—This occurs relatively often, either primarily or secondarily to a previous infection. It is usually unilateral, though an involvement of the other side may shortly follow the first. The infec-tion is often due to the use of a permanent urethral catheter, and may not appear until several days after the catheter has been removed. As a rule, fever and malaise precede the swelling by a day or two. Slight tenderness can be elicited from the beginning. Keeping the testes well supported is the best prophylaxis. During an attack, support with moderate pressure, an ice-bag and rest, if started early, will be all that is necessary. In most cases the pain begins to subside about the fourth day and the swelling several days later, though some thickening may persist permanently. Usually when the patient does not begin to im-prove by the fourth day, the condition will go on to suppuration. In

such cases drainage should be instituted as soon as any collection can be detected. Topical applications in the acute stage seem to do harm rather than good. Although vasectomy may reduce the occurrence, it does not preclude it. Heat in our experience has caused more pain and increased the suppuration.

Phlebitis.—This is rather infrequent, and the usual treatment of rest, elevation, bandaging, and heat are all that is necessary. When this condition occurs after prostatectomy, it is significant of lowered resistance to infection and is generally followed by other infectious complications. Ordinarily it is not necessary to keep these patients in bed after the first few days. Embolus has never been observed in our cases.

Cystitis.—Cystitis that is serious enough to be termed a complication should be relieved by preoperative treatment, and its recurrence after operation guarded against by thorough drainage and irrigations of boric-acid solution or weak permanganate.

Of the complications not directly attributable to infection, immediate or delayed hemorrhage is the most frequent.

Immediate Postoperative Hemorrhage.—This can usually be reduced to a minimum by careful hemostasis in the abdominal wound. When the patient leaves the operating table, the surgeon should be sure that there is no gross bleeding from the prostatic capsule. Sewing up the capsule, rubbing the inner surface until it contracts, packing a sponge wrung from boiling water tightly into the capsule for a minute, and lastly applying a gauze pack or Hagner bag will reduce the immediate bleeding to the point of safety. As little irrigation as is consistent with maintaining the tube free from clots seems to lessen the period of bleeding and to reduce the spasm of the bladder. The urine is usually free from gross blood by the second or third day.

Secondary or Delayed Hemorrhage.—This usually comes on from the fourth to the seventh day, and is due to the sloughing of prostatic tags. It occurs most often in patients who are otherwise feeling very well. There may be no pain or other premonitory symptom, and the first indication of trouble is a spasm of the bladder and expulsion, both by urethra and by tube, of clots and bright blood, the amount often apparently increased by an admixture of urine. This is most alarming to the patient. A hypodermic of morphin, an ice-bag, pressure to the perineum and removal of all tubes, as well as absolute rest, is all that is usually necessary in the way of treatment. In the past six years we have had but one serious hemorrhage from the bladder following prostatectomy.

In this case the treatment just described, as well as hot irrigations with astringent solutions, and the administration of horse serum, etc., served only to retard the bleeding somewhat, and the patient became pulseless and unconscious. Transfusion was then resorted to, and gave immediate and permanent results, followed by an uneventful convalescence. While the usual secondary hemorrhage is the slow gradual bleeding of a small vessel, I believe that a sudden, profuse, and dangerous hemorrhage might result from the sloughing through of a large vessel in the prostatic capsule. In such cases the bladder should be opened immediately and the bladder and capsule tightly packed with gauze without delay, and without attempting to find the vessel.

The danger from hemorrhage lies, however, not in death from loss of blood, but in the resulting susceptibility to infection in an anemic person of advanced age.

Cardiac Disease.—Heart complications, though frequently found in prostatic patients previous to operation, rarely have to be considered as postoperative complications except as a terminal condition, for cardiac decompensation or borderline cases can usually be detected before operation by means of a careful physical examination, supplemented, if necessary, by roentgen and electrocardiographic examinations. If compensation is good before operation, there is little to fear after operation from a chronic heart condition which rest and digitalis will not relieve.

Renal Insufficiency.—Uremia, thanks to preoperative treatment, is less frequent now than formerly. Two types must be recognized: (1) The acute congestion with suppression of urine; (2) the interstitial type, in which, though large amounts of urine may be voided, its specific gravity is very low and the elimination of toxic products almost negligible. The treatment of both types depends on early recognition and early effort to increase elimination by means of sweats, saline laxatives, liquid diet, rectal, subcutaneous, or intravenous salines, and caffein, spartein, or digitalis. Lack of appetite, restlessness, irritability, drowsiness, etc., may indicate renal insufficiency, and when such symptoms appear, the treatment should be pushed in order to get results. Twenty-four hours later, when vomiting, hiccup, coma, or delirium has developed, there is little to be accomplished. In these cases a careful, well-trained nurse saves many lives by recognizing the trouble and instituting proper treatment early. It has been our experience that complications and the consequent mortality may be reduced by efficiency and intelligent nursing. Formerly patients on whom prostatectomies had been

done were always attended by women nurses both for special and general care. As a rule these nurses had had little previous training, they despised this class of cases, they took no interest in the results, and only an embolus or a hemorrhage startled them into an appreciation of the presence of a complication when it was still early enough for effective treatment. The condition of the patients' wounds was evident from the fact that as far as possible cases of this kind were isolated, and justifiably, to one ward or hall. At present, with a corps of male nurses who spend practically all their time on prostatectomy and allied bladder cases, it is rare that a wound has an odor, and the patients occupy any room in the hospital. The male nurses are alive to the necessity of anticipating complications and starting the necessary treatment sufficiently early to do good.

Conclusions

I would emphasize:

1. The value of nurses who are trained in prostatic work.

2. The direct ratio between the local infection and the number and severity of complications.

3. The necessity of early recognition and early treatment of complications.

RESULTS OF MYOMECTOMY *

LEDA J. STACY

The ideal method of treating disease is that treatment which removes the pathologic lesion or relieves the symptoms and does not impair the normal function of the organ. This aim should be especially kept in mind in the treatment of uterine myomas.

Uterine myomas occur in 20 per cent. of all white women who have reached the age of thirty-five, and thus occur during the child-bearing period. In the series of 323 cases in which myomectomy was done in the Mayo Clinic from 1907 to 1914 inclusive, the average age of the patients was given as thirty-seven plus years, the youngest age, twenty-five years, and the oldest, fifty-nine years. Of these, 46+ per cent. were thirty years of age or under, and 70.9 per cent. were forty years of age or under.

Schauta,[1] in 1896, said that, as a rule, these patients do not become pregnant, and that when they do, they abort. Statistics show that pregnancy occurs in 2.6 per cent. of the cases of myomas, a percentage which is much less than the average for married women.

In our series, which is hardly a fair estimate because in many instances the myomas were essentially small, 51.9 per cent. of the 252 married women of the series had borne children. This percentage of pregnancies is much higher than that given by most writers. Twenty-eight per cent. of those who had borne children had had miscarriages also. Fifteen per cent. had had miscarriages only.

In a large percentage of cases, aside from the apparent interference with the normal function of the uterus, the myoma is a menace to the continued good health of the patient. According to Barrows,[2] 60 per cent. of all uterine fibroids take on an increase of growth at the menopause. Keen[3] states that the patient runs a risk of from 12 to 14 per cent. in carrying the tumor. Samuels is quoted by Keen as stating

that degenerative changes occur in as high as 64.9 per cent. of the cases, and develop after the fortieth year, a time when it was formerly thought that these tumors were likely to diminish in size. In our series, degeneration of the tumor had occurred in 17.8 per cent.

It has been shown more recently that circulatory changes are frequently found in cases of myoma. Boldt[4] noted such disturbances in 77 per cent. of his cases. Fleck[5] says that 133 of his 325 cases of myoma presented circulatory changes, and that in 46 of these there was no atypical bleeding. According to Barrows, the size of the tumor has no relation to the severity of the cardiac disturbance. The frequent association of hypertension and myomas is still a subject of discussion.

Up to the present time myomectomy seems to be the ideal treatment of myomas. While the x-ray and radium may later prove to be *the* treatment of choice, sufficient time has not yet elapsed to permit us to know their ultimate effect on the uterine and ovarian tissues and their function. Abbe[6] believes that later the x-ray and radium will be applied to a great many cases of this kind. Kelly and Burnam are using radium in most of their cases of myoma.

In the series of 323 cases here reported there were 226 abdominal and 57 vaginal myomectomies, with an operative mortality of 0.6 per cent. In 22.5 per cent. there was an elevation of temperature following operation, but no complications to prolong the convalescence beyond the usual time. Of the 226 abdominal myomectomies, 172 were done primarily for the removal of the myomas. In the remaining 94 cases the myomectomy was associated with some other pelvic operation. Multiple myomas were present in 38+ per cent. of the cases.

Letters were sent to the 323 patients and replies received in 203 instances. Six had died—cause not stated. A later hysterectomy had been performed in 7 cases, i. e., 3.4 per cent. of the patients heard from. A curetment had been done in 3 cases. The menopause had occurred during the interval since operation in 20 cases. Menstruation was reported as regular and normal in 85 per cent.; as profuse in 11.3 per cent.; and as scant and irregular in 16.3 per cent. The most interesting feature was the occurrence of pregnancy following the operation. There had been 6 miscarriages, 3 occurring in one woman. Normal full-term pregnancy had occurred 18 times. One patient who had been married three years before the operation without having been pregnant had three full-term pregnancies and one miscarriage following the operation. In 5 other cases of sterility before the myomectomy normal pregnancies

occurred following operation. One patient who had had a previous miscarriage had a normal full-term pregnancy after operation. There were 4 cases of pregnancy at the time of myomectomy and these continued to full term.

In view of these findings, in cases of myomas in women under thirty-five years of age, and when it is possible to reconstruct a fairly normal uterus, myomectomy should be seriously considered before a hysterectomy is decided upon. At least the patient should be given the opportunity of choosing between a hysterectomy and a myomectomy, fully understanding the possibility that a future operation may be necessary.

REFERENCES

1. Schauta, F.: Quoted by Keen, *loc. cit.*
2. Barrows, C. C.: "Remarks on Uterine Fibroids with Special Reference to Their Relation to Tumors of the Thyroid Gland," Amer. Jour. Obst., 1914, lxix, 33–43.
3. Keen, W. W.: Surgery, Philadelphia, Saunders, 1913, pp. 850–855.
4. Boldt, H. J.: "Uterine Myofibromata and Visceral Degeneration," New York Med. Jour., 1905, lxxxii, 887–893. Quoted by Barrows, *loc. cit.*
5. Fleck, G.: "Myom und Herzerkrankung in ihren genetischen Beziehungen," Arch. f. Gynäk., 1904, lxxi, 258–287. Quoted by Barrows, *loc. cit.*
6. Abbe, R.: "Uterine Fibroids, Menorrhagia and Radium," Med. Rec., 1915, lxxxvii, 379–381.

CANCER OF THE UTERUS: ITS SURGICAL TREATMENT *

DONALD C. BALFOUR

The history of cancer of the uterus, and particularly of the cervix, reveals a greater number and variety of therapeutic measures advocated for its treatment than have been suggested for cancer in any other situation. Cancer of the lip, stomach, colon, rectum, etc., although still the subject of profitable consideration from an operative standpoint, is treated according to principles well established, and further progress will probably be in technical and diagnostic refinement rather than in the adoption of radically new methods.

That cancer of the cervix presents quite a different problem is obvious from the many publications on the subject, the new treatments advanced, the modifications of old methods, and the repeated discussion of the relative merits of those now in use. This is evidence, not only that the profession is dissatisfied with the results obtained in the past, but that, conversely, judging by temporary results, cancer of the uterus does respond readily to various measures.

The disease is characterized by certain features and associated with conditions which result in serious obstacles toward increasing the efficiency of surgical or any other treatment. The irregularity, and frequently the subtleness of the onset of symptoms, the inaccessibility of the disease area, its septic character and the variability in its virulence, a hesitant and pessimistic public, and the failure of a part of the profession to realize their responsibility, are the chief factors retarding the best efforts to combat the disease.

The low operability rate is, therefore, easily understood. I believe no surgeon or clinic in this country is fortunate enough to see even 50 per cent. of their cases at a stage when a radical operation is possible.

In the Mayo Clinic during the past ten years about 44 per cent. were found to be operable. European surgeons are favored by a slightly higher percentage, Wertheim,[1] for example, reporting 55 per cent.

Although other factors have contributed to this more encouraging situation, it must be credited in large part to the energetic and persistent educational campaign originated by Winter. It may be confidently expected that signs of an increasing operability rate will soon be evident in America. Wide and repeated publicity should be made of the fact that in this country alone more than 12,000 women die from uterine cancer each year, and that in practically every instance the disease had produced symptoms at a stage in which a positive diagnosis could have been made and a cure obtained. The importance, therefore, of making it possible to attack the disease at that stage is obvious, and it is to be hoped that within the next few years uterine cancer will be dealt with in the same scientific and organized manner as tuberculosis, typhoid fever, smallpox, influenza, etc., and that the methods so successfully employed in educating the public in general health problems will be applied to this disease.

The subtleness of the onset of uterine cancer makes it imperative that its salient features be repeatedly brought to the attention of the public and the profession. Emphasis should be laid on the fact that it is vital to investigate promptly and thoroughly any menstrual irregularity or vaginal discharge. At the first opportunity it is important that in every instance bimanual examination and careful observation of the cervix with good light should be carried out, rather than that the significance of menstrual disturbances should be minimized. Moreover, if there is the least doubt as to the presence of malignancy, a specimen should be excised from the eroded cervix for microscopic examination, or a diagnostic curettage should be performed, to be followed immediately by appropriate treatment should malignancy be demonstrated. If such a plan were followed, it would produce an immediate increase both in the number of operable cases and in the percentage of surgical cures. The patients who are usually prompt in seeking advice are those who, some years past the menopause, are alarmed by the occurrence of a uterine hemorrhage. It is rather the rule that the serious import of such a symptom is realized by the patient at once, and the further responsibility must be assumed by the physician or surgeon.

The treatment of cancer of the fundus of the uterus may be dismissed in a word, insofar as the choice of operation is concerned. Fortunately

cancer of the uterine body is usually found to be operable, and the results of its surgical treatment compare favorably with the results of treatment of cancer in any other situation. Total abdominal hysterectomy is unquestionably the operation of selection. Vaginal hysterectomy, however, is a valuable alternative, and should be advised when the patient, by reason of marked obesity, cardiorenal disease, anemia, pulmonary lesions, etc., is a poor surgical risk.

A study of cancer of the cervix, however, both in its uninterrupted course and in the results of its operative treatment, reveals a decided variability in malignancy. For this variation several factors are responsible. One of the most important is the resistance toward the progress of malignant disease which patients of themselves possess, and which, though very inconstant, undoubtedly governs both the duration of the disease and the results of treatment considerably. For practical purposes, however, until it is known on what this resistance depends or how it may be increased, this factor may be disregarded.

The most important factor, at least from the standpoint of treatment, by which this variability in malignancy appears to be influenced, is the character and degree of infection in the carcinomatous process. Though the extent of the sepsis cannot be accurately estimated at the primary examination, this septic factor determines the result of any form of treatment more than is realized. Further, the gross evidences of the disease may lead to an erroneous impression as to its vulnerability to treatment and the ultimate prognosis. Not infrequently an extruding growth of the cauliflower type, large enough to fill the vagina, will lend itself so satisfactorily to appropriate local treatment that a total hysterectomy can be done later with fair possibility of cure. On the other hand, from the appearance of the cervix the disease may be considered to be in an early stage and only when a radical operation is undertaken is it discovered that the cervix is extensively invaded and the disease so advanced that there is little prospect of cure.

It is apparent, therefore, that there can be no arbitrary divisions in cancer of the cervix, and any classification, particularly in its application to prognosis, is of only relative accuracy. Nevertheless, the treatment of the disease must be adapted to its apparent stage and the condition of the patient, so that a thorough familiarity on the part of the surgeon, with all the methods of recognized value at his disposal, is advisable. For our present purposes cases may be grouped as follows:

1. *Advanced Stage.*—This group includes cases in which the involve-

ment is so great that there can be no question as to the impossibility of entirely removing the diseased area by surgical measures, at least in a primary operation.

2. *Moderately Advanced Stage.*—Borderline cases in regard to which there may be a legitimate discussion as to the advisability of attempting a primary radical operation. Such are cases in which the disease has encroached slightly on the vaginal walls, cases of early broad-ligament involvement, and those of extensive cauliflower growth with the rim of the cervix firm and uninvaded by the disease.

3. *Early Stage.*—Cases in which the disease is limited to the cervix and is not of the rapidly infiltrating type.

Between 55 and 60 per cent. of the carcinomas of the cervix seen at the Mayo Clinic are of the advanced type. It is usually quite obvious that they are not surgical in the sense that the disease may be extirpated satisfactorily. However, for such cases there are other means from which, when used intelligently and earnestly, positive benefit may be derived. I refer to the ligation of the blood supply and the use of heat, radium, and deep roentgen-ray exposures. These measures separately or in combination usually ameliorate the symptoms, retard the progress of the disease, and improve the health of the patient, often for a considerable period. In many instances the change is remarkable, and in a few there may be enough destructive action on the growth, with sufficient subsequent mobilization of the uterus, to make its radical removal possible.

At the present time, in hopelessly advanced cases in which palliative measures seem advisable, we advocate: (1) The use of heat after the Percy method, coupled in suitable cases with ligation of the internal iliac and ovarian vessels, or (2) radium, or (3) acetone, when circumstances necessitate other treatment.

It is unnecessary to refer in detail to the method of using the electric cautery, but the experience of others, particularly Clark, of New Orleans, and our own experience in more than one hundred cases confirm the claim of Percy,[2] viz., that a moderate heating process, maintained for a long time, is more efficacious than a rapid burning with a high degree of heat. The former methods of using heat in advanced cancer of the cervix often gave remarkable results, but both theoretically and practically the method of Percy is more efficient. Criticism of this slow heating process is usually based on deductions made from a small number of cases and often on observations that are inaccurate by reason of

failure to follow out the detail of the method. It is true also that too much has been expected of it. Although we have no reason for doubting that a cure can be obtained by the treatment in some very suitable cases, we have never depended on such treatment alone if the uterus could be removed subsequently with any degree of safety. Similarly, any other form of treatment which does not presuppose a subsequent hysterectomy is open to criticism. In regard to the use of the Percy method of heating I would emphasize the fact that the abdomen should always be opened. The only accidents which have occurred in my own experience (vesicovaginal fistulas in two cases, and ureteral fistula in one) took place when I failed to open the abdomen.

Our experience with radium has been too short to warrant speaking definitely, but already it has been proved of benefit in the advanced cases in which we have used it, and appears to be of value in the treatment of recurrences. Recently, for purposes of comparison, we have been using radium and heat in apparently parallel cases and we hope that we may thereby be able to contribute some aid toward determining their relative merits in advanced cases.

The application of radium in carcinomas of the cervix must be done with care, as authorities have shown that the rectum is easily injured and the disease may be actually aggravated. Kelly and Burnam,[2] who have had the most extensive experience in this country, report on 213 cases, 14 of which they considered operable and 199 inoperable. Of the latter, 53 patients have been clinically cured, 109 markedly improved, and 37 not improved. From these results Kelly and Burnam conclude that if there is no evidence of general metastasis, one in four cases of inoperable cancer of the cervix may be cured by radium.

In the moderately advanced stage of the disease the main factors influencing the selection of treatment are the immediate operative risk and the prospect of cure. In the Mayo Clinic during the past two years a preference has been developed for a two-stage method of dealing with these borderline cases.

It has been repeatedly demonstrated in cases of cancer in many different parts of the body that cancer-cells will easily implant themselves on freshly cut and raw surfaces. Accordingly, it has become an established rule that the utmost care must be used in the handling of cancerous growths. Frequently there is failure to appreciate this necessity in the operative treatment of cancer of the cervix, and even with the most scrupulous care in some instances it is impossible, unless the

growth has first been sterilized, to manipulate and remove the uterus without great risk of cancer-cell implantation.   Moreover, it cannot be too strongly emphasized that in many women dying of cancer of the cervix the growth is still localized and death has resulted more from hemorrhage and chronic sepsis than from the actual cancer.   The virulence of the disease, therefore, is dependent largely on the virulence of the infection.   If, in following the methods of dealing with cervical cancer, full cognizance is taken of the possibilities of implantation and the rôle of infection, local recurrences and failure to cure would be much less frequent.   As a general principle, therefore, practically all radical extirpations should be preceded by the thorough sterilization of the local disease.

It is mainly on account of its sterilizing effect that heat has been so efficient in limiting the progress of cancer.   The part that sepsis plays is constantly observed in the great improvement following such treatment, and the results are an obvious argument in favor of the two-stage operation.   The improvement is both local and constitutional.   In many instances the gross evidence of the disease can be entirely destroyed, and the discharge and bleeding stopped.   When the latter have produced constitutional disturbances, coincident with such local improvement the general condition of the patient undergoes remarkable change, the gain in weight, strength, and color, and the relief of pain being rapid.   As a result, the risk of the radical operation is correspondingly lessened. Moreover, the entire cervical body has been sterilized, and it is suggestive that in several instances in which a hysterectomy has later been done cancer-cells have not been demonstrable in any part of the removed uterus.

The results obtained with heat are rather directly dependent on the degree of thoroughness with which the treatment is carried out.   Radium and mesothorium may serve a similar purpose, and Kelly believes that three out of four apparently hopeless cases of cervical cancer can be cured by the combined effect of radium and operation.   Therefore, in the majority of cases of a moderately advanced stage of the disease the cervix should first be thoroughly sterilized, and then, unless there is some definite contraindication, a total abdominal hysterectomy should be performed, usually at the end of three weeks or three months.   In some instances it may be advisable to follow the local treatment immediately by total hysterectomy.   When conditions are such that the abdominal operation is inadvisable, sterilization of the growth, with

immediate vaginal hysterectomy, preferably by the clamp and cautery, is a procedure of decided value. Rarely it may appear advisable to depend entirely upon treatment by heat or radium.

In speaking of total abdominal hysterectomy, I am aware that surgeons differ in their conception of the extent of the operation, but I believe there is an apparent tendency in this country, among men of considerable experience, to abandon the so-called Wertheim operation. Although this operation offers the best opportunity for eradicating the disease, its employment as a routine is open to serious question. Even in the hands of the most experienced surgeon, it carries an initial mortality of from 12 to 20 per cent., and in non-selected groups of cases this percentage is considerably higher. Moreover, the disadvantages of a typical Wertheim hysterectomy are not concerned entirely with immediate operative mortality, for with it ureteral, vesical, and rectal fistulas and other complications are reported in about 10 per cent. of the cases. While any operation as extensive as the Wertheim type is perhaps sound theoretically, it is quite beyond the ability of the average surgeon, and even the most competent surgeon subjects an enfeebled patient to a high operative risk.

With a primary mortality of from 20 to 25 per cent., we cannot expect any method of educating the public to the necessity of the early operative treatment of uterine cancer to produce marked results; and the American public may quite legitimately hesitate to support such a dangerous surgical method where there are such risks of distressing sequelæ even if the patient survives the operation. Such a high mortality might be accepted by the public if the disease were of an acute character and associated with symptoms that impressed the patient with its seriousness, the urgency of operative measures, and the risk of delaying treatment. In uterine cancer, however, the patient is not incapacitated, and there is nothing to indicate either to her or her friends that an operation of such great risk is warranted. The readiness with which the public will seek operation for goiter, gallstones, acute appendicitis, and cancer in other situations, particularly cancer of the breast, is due largely to the fact that the immediate operative mortality is low.

The basis, therefore, of a successful propaganda against uterine cancer must be a lowering of the operative mortality and a lessening of secondary sequelæ. The increase in the percentage of permanent cures will depend not so much on the character or the extent of the operation as on the opportunity of dealing with the disease in its early stages, and

every effort should be made to keep the public from being prompted to delay by a mortality which is forbidding. Although it may be argued that success has been achieved in Germany in spite of a high operative mortality, a campaign under such conditions would not be enthusiastically advanced by American surgeons and would not be readily accepted by the American people.

It has now been proved beyond a doubt, as the result of careful judgment in regard to the method of operation, discretion as to the extent of the radical operation and recognition of factors heretofore not sufficiently appreciated, that the operative mortality of cancer of the uterus can be kept low, and that the end-results will compare favorably with those following a routine operation of more risk.

From an operative standpoint the greatest obstacle is the inaccessibility of the disease. Frequently the body of the uterus is carefully extirpated, while in the immediate region of the disease all the surgical principles for the treatment of cancer are disregarded. Heidenhain[4] has shown that in the removal of a carcinomatous growth the dissection should not reach within three centimeters of the visible limits of the growth. However, in cases in which there are extensive glandular involvement, broad-ligament infiltration, and a friable cervix, an actual radical extirpation based on such principles is impossible.

I am certain not only that the primary operative mortality would be lessened, but also that the number of permanent cures would be increased by a more frequent employment of the two-stage operation, providing a sincere effort were made in each case to utilize the advantages offered by the various methods at our disposal. While the development of one particular method to the exclusion of all others may result in operative dexterity and a degree of improvement in one's own results, it is not a rational attack on the disease.

The treatment of cases of early carcinoma of the cervix, which constitute a relatively small group, is a lesser problem, yet there may occasionally be some doubt as to the most suitable method. It is questionable, for instance, whether in this stage of the disease there is ever any justification for treatment other than radical extirpation of the uterus. Heat, radium, etc., have no place in the treatment of cases of this kind unless some exceptional circumstance prohibits abdominal hysterectomy. Even those patients who are such poor surgical risks that the abdominal operation is inadvisable may be reasonably safe risks with vaginal hysterectomy. This latter operation, by the clamp

and cautery, is associated with a low operative mortality, and with in-
telligent selection of cases and adherence to correct surgical principles it
yields a percentage of cures as high as that obtained by total abdominal
hysterectomy.

The practice of packing gauze in the pelvis for drainage in total
abdominal hysterectomies should be condemned. Undoubtedly gauze
lying against a ureter or bladder already stripped has produced fistula
that otherwise would not have occurred. For some time, therefore, we
have discontinued the use of gauze in the pelvis in such cases unless it
was demanded by emergency.

Although recently the operative treatment of recurrences following
a radical extirpation of the uterus has been urged by some, it has not
been looked upon with favor by the majority of surgeons. Zweifel[5]
particularly has employed the results of radical operation for recurring
malignant disease to support arguments in favor of secondary opera-
tions. However, while the statistics are taken to indicate that life has
been prolonged, we know that frequently patients live well up to the
five-year limit before they die of the disease. Secondary operations for
cancer in other parts of the body have not been followed by results
sufficient to encourage such efforts. On the other hand, we have seen
distinct temporary benefit in these recurrences from the use of heat and
radium. With either of these methods greater care must be taken in the
treatment of such cases than in the treatment of those in which the
uterus has not been removed.

In conclusion the treatment of cancer of the uterus should be as
follows:

1. In early cancer of the cervix thorough cauterization, followed
immediately by a total abdominal hysterectomy. The latter should be
as radical as is consistent with the character of the case and the ability
of the surgeon. In a small percentage of cases the condition of the
patient may demand a vaginal hysterectomy as the wiser procedure.

2. For moderately advanced cases the use of heat by the Percy
method. The surgeon must then decide, from the results of this treat-
ment, whether a total abdominal hysterectomy is advisable and when.
Vaginal hysterectomy should be considered if the patient is a serious
operative risk.

3. In advanced cases a determined effort to ameliorate the symp-
toms and prolong life by heat, radium, etc., is occasionally rewarded by
a result which permits of radical operation.

REFERENCES

1. Wertheim, E.: "Le cancer de l'utérus 'col et corps'; technique de l'opération et efficacité," Ann. de gynéc. et d'obst., 1913, 2. s., x, 502–506.
2. Percy, J. F.: "A Method of Applying Heat Both to Inhibit and Destroy Inoperable Carcinoma of the Uterus and Vagina," Surg., Gynec. and Obst., 1913, xvii, 371–376. "Inoperable Uterine Carcinoma, a Method of Applying Heat in its Treatment," Boston Med. and Surg. Jour., 1915, lxxiii, 93–95.
3. Kelly, H. A., and Burnam, C. F.: "Radium in the Treatment of Carcinomas of the Cervix Uteri and Vagina," Jour. Amer. Med. Assoc., 1915, lxv, 1874–1878.
4. Heidenhain, L.: "Ueber die Ursachen der localen Krebsrecidive nach Amputatio mammæ," Arch. f. klin. Chir., 1889, xxxix, 97–166.
5. Zweifel, E.: "Dauererfolge nach Rezidivoperationen bei Uteruscarcinomen," Arch. f. Gynäk., 1914, cii, 411–431.

INTRACANALICULAR PAPILLOMA OF THE BREAST *

EDWARD STARR JUDD

The characteristic feature of intracanalicular papilloma of the breast is a bloody discharge from the nipple. Often this is the only symptom; the tumor cannot be palpated, and may even be difficult to locate when the breast is sectioned. Greenough and Simmons[1] state that papillary cystadenoma, villous papilloma, or duct cancer in which gross intracystic papillary growths occur, accompanied often by a bloody discharge from the nipple, should be considered as true local tumor formations which have a very high predisposition to carcinoma. Lewis[2] states that the pathologic processes associated with the discharge of hemorrhagic or serohemorrhagic material from the nipple should be classified in two groups: Group I, abnormal involution associated with serohemorrhagic discharge; and Group II, small papillomas within the milk-duct deep within the breast tissue, no tumor being palpable.

Intracanalicular papilloma may be located at any point in the milk-ducts. In one of our cases a tumor with a long pedicle had prolapsed from the nipple and gave the impression of a papilloma, although careful examination showed that it was not attached to the nipple. Such tumors are usually painless and have no skin attachment. They have been reported as occurring between the ages of nineteen and eighty-one, although I think they are more common past middle life. Trauma and child-bearing are not factors in producing them. In very few of our cases of true intracanalicular papilloma have we been able to distinguish a tumor or palpable thickness in the breast. However, Erdmann[3] states that at times the condition is so well marked as to be readily recognized as a tumor, and for this reason an erroneous diagnosis of simple cystadenoma may be easily made.

The discharge varies in amount and may be intermittent. Usually

it is slight and comes in drops, although frequently a considerable quantity can be forced out by pressure on the breast. The fluid is odorless, sticky, and stains the dressing a pale yellow. A discharge accompanying a carcinomatous condition of the breast is more watery, darker in color, greater in amount, and often has a distinct, rather foul odor. The discharge due to papilloma often contains epithelial cells from the milk-ducts. Erdmann mentioned one case in which many streptococci were found in the fluid. The thick, colorless discharge associated with chronic mastitis often contains degenerated cells.

The papillary outgrowths arise from the wall of the milk-duct. They have a branching, vascular connective-tissue stalk supporting a large growth of epithelium in the form of villous projections and glandlike interlacing tubules. The epithelium does not infiltrate the surrounding tissue. If a tumor is present, it will be found in the central part of
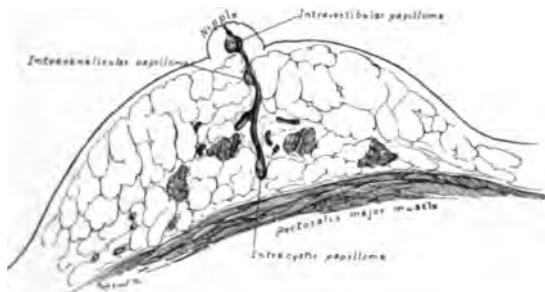
Fig. 224.—Diagram of breast, showing different placements of papillomas.

the breast, usually just under the nipple. These papillomas may be multiple, and there may be many tumors in the breast. The epithelial layers of the tumor may be composed of a single layer of columnar cells or several layers of cuboidal cells. In papillary cystadenoma we do not know whether the papillary outgrowth is a process secondary to the formation of the cyst. It would seem that intracanalicular papillomas and papillary cystadenomas were separate processes. Certainly, the symptoms from an intracanalicular papilloma may exist for many years and yet there may be only the single papilloma in the duct and no evidence of cyst formation except perhaps a slight dilatation of the duct. The only difference between intracanalicular papilloma and papillary cystadenoma would seem to be in the place of origin. Intracanalicular papillomas arise from the walls of the milk-ducts, while papillary cystadenomas originate in the walls of the acini. Intracanalicular papil-

lomas are more frequently found as single growths on a pedicle, while a cystadenoma is usually composed of a number of interlacing papillomas. Papillary cystadenomas often attain considerable size and form a palpable tumor-mass or frequently multiple tumors.

Bleeding from the nipple was at one time considered almost pathognomonic of cancer, and many radical operations have been performed on that basis alone. The more recent teachings of Bloodgood,[4] Lewis, and others would seem to show that bleeding without tumor is more apt to be a symptom of a benign condition than of malignancy. Bloodgood states that bleeding from the nipple without the presence of a palpable tumor of the breast is not an indication for operation. He reports that he has had under observation for some time 12 cases of bleeding nipple which he considers are intracanalicular papillomas because there is no tumor-mass. These patients have had no treatment, and with most of them the discharge ceased at the end of a few years. However, in one case on record the discharge continued for twelve years. In one case reported by Lewis malignant changes were found in what was primarily an intracanalicular papilloma. This is

Fig. 225.—Breast enlarged four times: *a*, Intravestibular papilloma; *b*, intracanalicular papilloma; *c*, intracystic papilloma; *d, d, d, d,* pedicles.

the only case of which I have been able to find record in which these changes have been observed. The patient had a bloody discharge from the nipple for three months. Lewis states that a diagnosis of malignancy could

Fig. 226.—Carcinoma near the base of the nipple, showing nipple retraction.

Fig. 227.—Extruded papilloma of the nipple.

not be made from the nature of the tumor or the character of the discharge, as the lesion did not differ in these respects from a papillary cystadenoma. The granular wall of the cyst, however, aroused suspicion and was shown to be malignant. Erdmann reports two cases in his series which, from

'16—30

gross appearances, he thought were malignant, but his pathologist reported that they were benign. The pathologist, however, made a notation that there was an atypical proliferation of the epithelium and that they were suspicious. Greenough and Simmons report three malignant cases in a series of 20 cystadenomas.

I have recently reviewed 100 consecutive cases of discharging nipples. I found 50 in which a serohemorrhagic discharge was present, and 50 which had other forms of discharge from the nipple.

In the first group of 50 I found the following pathologic conditions associated with bleeding nipple: Twenty-seven patients (54 per cent.) had carcinoma of the breast: 12 (24 per cent.) had chronic cystic mastitis; 8 (16 per cent.) had intracanalicular papilloma. In three cases (6 per cent.) the early discharge seemed to be a serohemorrhagic oozing from the nipple which later proved to be Paget's disease.

In the second group of 50 cases, which includes those in which there were various kinds of discharges, exclusive of the hemorrhagic type, I found 30 (60 per cent.) to be breast carcinomas; 14 (28 per cent.), chronic cystic mastitis; 4 (8 per cent.), intracanalicular papilloma. Two cases (4 per cent.) proved to be simple cysts.

	50 cases serohemorrhagic discharge from the nipple		50 cases other forms of discharge from the nipple	
	CASES	PER CENT.	CASES	PER CENT.
Carcinoma	27	54	30	60
Chronic cystic mastitis	12	24	14	28
Intracanalicular papilloma	8	16	4	8
Paget's disease	3	6	..	..
Simple cyst	..	..	2	4

SYMPTOMATOLOGY

Group I, Bleeding Nipples.—A tumor was present in each of the 27 cases of carcinoma. The first symptom in 22 of the 27 was a tumor; in the remaining 5 cases it was a discharge from the nipple. Fourteen of the 27 patients complained of pain in the breast. Twenty-three patients out of the 27 had undergone lactations. The average duration of the discharge was ten months; the average age of the patients, fifty-four years.

A tumor or palpable thickening in the breast was present in 7 of the 12 cases of chronic cystic mastitis. In 9 of the 12 the first symptom was discharge; in 3 it was pain. However, only 4 of the 14 patients complained of pain at any time. Eight of the 12 patients had undergone lactations. The average duration of the discharge was ten months; the average age of the patients, fifty years.

A palpable tumor was present in 4 of the 8 cases of intracanalicular papilloma. Nipple discharge was the first symptom in each of the 8

cases.   Three of these patients had undergone lactation.   The average
duration of the discharge was about four years;   the average age of the
patients, forty-seven years.

In the 3 cases of Paget's disease the early symptom of serohemor-
rhagic oozing from the nipple was later followed by ulceration and
crusting.

Group II, Non-hemorrhagic Cases.—A tumor was present in 29 of
the 30 cases of carcinoma in this group.   In the one instance in which
the clinician was unable to palpate a tumor the carcinomatous growth
was small, involved the area directly beneath the nipple, and could
easily have been missed.   Tumor was the first symptom noted in 23 of
the cases;   in the remaining 7 it was discharge.   Pain was present in 26
of the 30 cases.   The average duration of the discharge was thirteen
months;   the average age of the patients, fifty years.

A tumor was present in 13 of the 14 cases of mastitis.   The case in
which a tumor was not palpated was that of a woman who four years

Fig. 228.—Cross-section of extruded papilloma of the nipple.

previously had had a tumor removed from the breast and whose com-
plaint at the time we examined her was pain and an intermittent, glairy
mucoid discharge.   Tumor was the first symptom in 5 cases;   discharge
in 4;   and pain in 5.   Ten of the 14 patients complained of pain.   Ten
patients had undergone lactation.   The average duration of the dis-
charge was eighteen months;   the average age of the patients, forty-six
years.

A tumor was present in 3 of the 4 cases of intracanalicular papilloma.
The first symptom in each of the 4 cases was discharge from the nipple.
Pain was present in 1.   All of the 4 patients had undergone lactation.
The average duration of the discharge was three years;   the average age
of the patients, fifty-two years.   These cases really belong to the
hemorrhagic group, as the discharge was variously described as chocolate-
colored, dirty-brown, etc., showing that hemorrhage had taken place in
the cysts at some time or other, but had been retained and had undergone
changes.

A tumor was present in both of the 2 cases of simple cysts.   In one the

first symptom was tumor; in the other, discharge. The discharge was described as milky or yellowish in appearance.

Recently, in reviewing our 32 cases of papillomas of the breast, I found the following pathologic classification: Intracystic papilloma, 8; intracystic carcinomatous papilloma, 8; intracanalicular papilloma, 10; carcinomatous intracanalicular papilloma, 3; intra-acinar papilloma, 1; intracanalicular papilloma associated with a carcinoma of the breast, 2. In this series carcinoma was present in 11; in 3 other cases the pathologist believed the condition was carcinomatous but was unable to make a definite diagnosis.

The characteristic symptom in these 32 cases was bleeding, or a serohemorrhagic discharge from the nipple. In a few instances there were palpable tumors, but in all of these the growth was produced by chronic mastitis or by cystadenoma and in no instance was there a papilloma in the duct large enough to be palpated except in one case in which it extruded from the nipple.

This review of 100 cases of discharging nipples would seem to confirm former reports on the subject. Carcinoma appears to be the most common lesion producing a discharge from the nipple, but it is almost invariably associated with a tumor in the breast. Tumor is usually present some time before the discharge begins. In some of our cases of chronic cystic mastitis the discharge may have been from a duct papilloma, for often these tumors are very small and might easily be overlooked. This series also seems to lend evidence to the contention that a hemorrhagic or serohemorrhagic discharge from the nipple in the absence of a palpable tumor is most often produced by benign intracanalicular papillomas. In view of this fact treatment should be conservative, especially in young women. In older women, particularly if the condition is associated with chronic cystic mastitis, the best procedure would seem to be the removal of the mammary gland. If there are evidences of malignant change, a radical operation should be done.

REFERENCES

1. Greenough, R. B., and Simmons, C. C.: "Papillary Cystadenomata of the Breast," Ann. Surg., 1907, lxiv, 188–202.
2. Lewis, D.: "Bleeding Nipples," Surg., Gynec. and Obst., 1916, xxii, 666–671.
3. Erdmann, J. F.: "Intracanalicular Papilloma of the Breast," Amer. Jour. Surg., 1912, xxvi, 208–210.
4. Bloodgood, J. C.: "Cancer Cysts of the Breast and Their Relation to Non-malignant Cysts," Jour. Amer. Med. Assoc., 1909, liii, 1475–1479.

TUBERCULOSIS OF THE BREAST *

A REPORT OF 10 CASES

LUIGI DURANTE AND WILLIAM CARPENTER MacCARTY

In a previous contribution to the knowledge of tuberculosis of the female breast, one of us (Durante[1]) reviewed the bibliography of the subject to January, 1914, and discussed the anatomic forms, histogenesis, symptoms, and therapy. This paper appeared contemporaneously with the excellent and extensive contribution upon the same subject by Deaver[2] and Herman.

Since January, 1914, four other papers by Leriche,[3] Pirrung,[4] Roffo,[5] and Miles[6] have appeared and described two types of mammary tuberculosis, namely, the "sclerotic" and "inflammatory" types.

A review of the literature reveals the following important points:

1. The period of apparent greatest susceptibility to mammary tuberculosis is between the twentieth and fortieth years of life. The condition has been found only twice in the female breast before puberty and only ten times in the male breast. A total of 180 cases of all types in the male and female have been reported.

2. Many terms, such as "disseminating," "confluent," "miliary," "nodular," "abscess," "sclerotic," and "inflammatory," have been applied to the various aspects of the condition.

Retraction of the nipple has been reported and is, therefore, a sign which might be readily confused with a similar characteristic of mammary cancer.

3. Seventeen cases (Klose[7]) have been reported in association with neoplastic processes. Practically all observers attributed no relation between the two conditions.

4. The localization of the infection in the breast through an abrasion of the skin, although a possibility, has been considered a remote probability.

5. Practically every case presented itself as a secondary localization from a primary focus in some other portion of the body.

6. In the cases which have been reported the most plausible mode of infection was by contiguity with pleural or costal tuberculosis or through blood- or lymph-stream.

Fig. 229.—(52,798.) Tuberculosis of the axillary and pectoral lymphatic glands. A, Breast; B, pectoral lymphatic; C and D, tuberculous glands in the breast.

7. All observers considered the blood-stream to be the most common route of infection.   In some cases, however, no tangible primary focus was discovered.

8. In certain cases the organism was apparently carried reversely from the cervical or axillary lymphatic glands, which were demonstrably

tuberculous. Some cases were attributed to an infection of the retrosternal lymphatics which follow the collateral branches of the internal mammary artery. Mammary tuberculous infections which were secondary to axillary lymphatic involvement on the same side were described by Duret,[8] Verneuil,[9] Berchtold,[10] Salomóni,[11] Caminiti,[12] Scott,[13] Schmidt,[14] Duvergey,[15] Vignard and Pasquier,[16] Putzu,[17] Leriche,[3] Roffo,[5] and Durante.[1] Scott,[13] Bahuand,[18] Braendle,[19] and Cignozzi,[20] described the condition as secondary to cervical lymphatic involvement.

In the Mayo Clinic from 1904 to 1915 there have been 10 cases (0.51
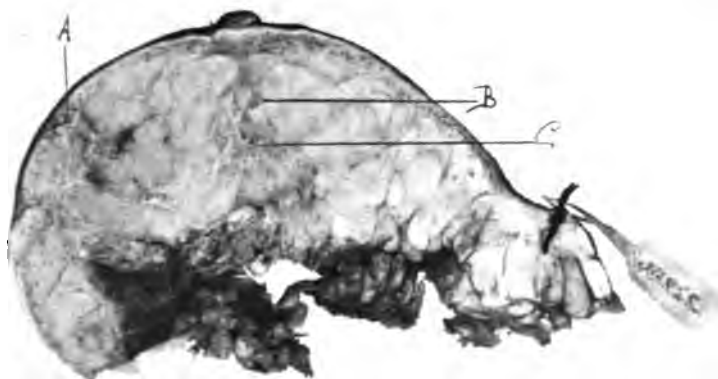
Fig. 230.—(63,635.) Tuberculosis of the breast, apparently produced by retrograde diffusion from tuberculous axillary adenitis. *A*, *B*, and *C*, tuberculous areas.

per cent.) of mammary tuberculosis in a series of 1933 pathologic mammary conditions.

Deaver[2] found 0.83 per cent., Scott,[13] 1.4 per cent., and Bloodgood,[21] 0.6 per cent., of their mammary specimens tuberculous.

In the 10 cases observed by the writers there were 3 in which no primary focus was clinically demonstrable; there were 3 associated with tuberculosis of the lungs and 3 cases associated with no clinical tuberculous lesion other than tuberculosis of the axillary lymphatic glands, and one which was associated with a pleurocostal lesion.

The gross pathologic picture is one of chronic mastitis characterized by a dirty discoloration of the normally pearly-white glandular tissue,
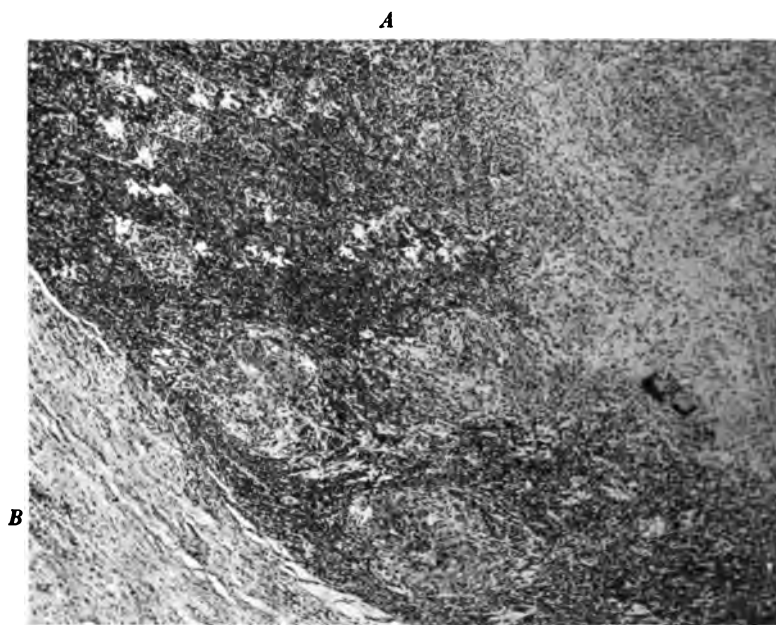
Fig. 231.—(52,798.) Photomicrograph (×50, Unna-Pappenheim stain). Zone of division between tuberculous nodule, A, and parenchyma of the breast, formed by a barrier of dense connective tissue, B. The section was taken from Point D, Fig. 229.
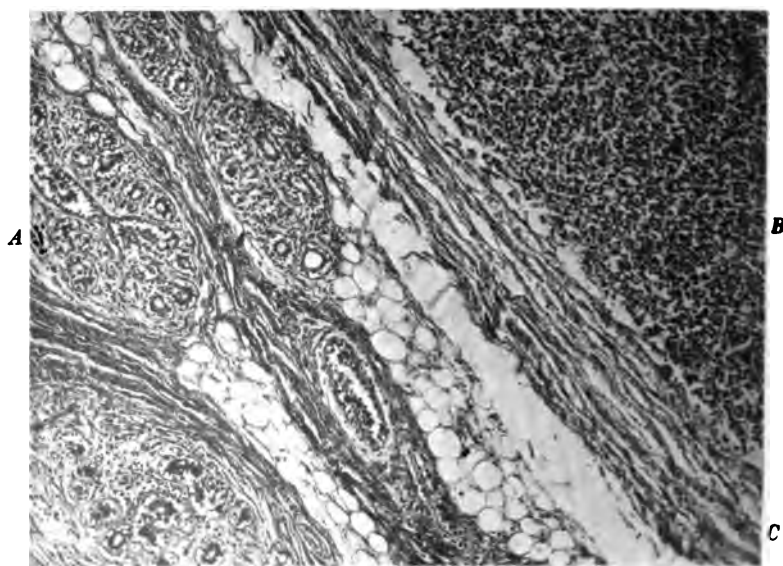
Fig. 232.—(52,798.) Photomicrograph (×60, Unna-Pappenheim stain) showing zone of division between tuberculous nodule, B, and the parenchyma of the breast, A. A, primary hyperplasia (MacCarty) of mammary acini, surrounded by connective tissue and a slight lymphocytic infiltration; B, margin of tuberculous nodule; C, barrier of connective tissue dividing mammary parenchyma from tuberculous nodules. The section was taken from Point C, Fig. 229.
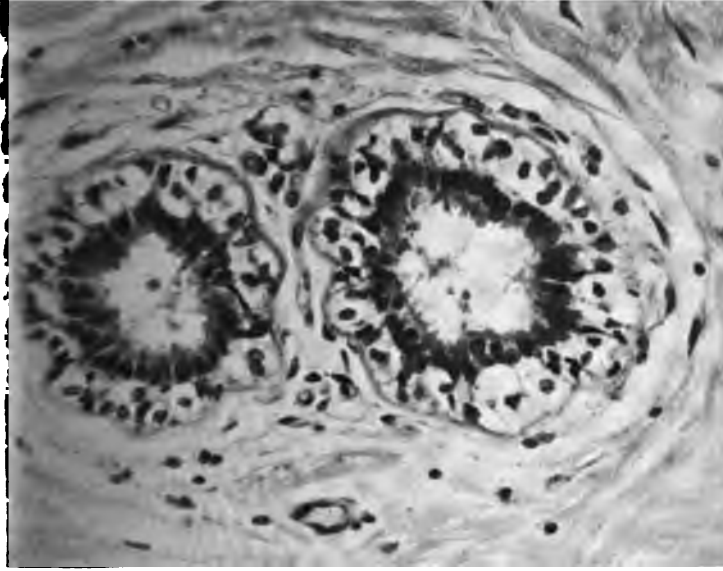
Fig. 233.—(52,798.) Photomicrograph (×120, Weigert-Van Gieson stain) showing primary hyperplasia (MacCarty) of mammary acini and connective-tissue reaction at Point E, Fig. 229.
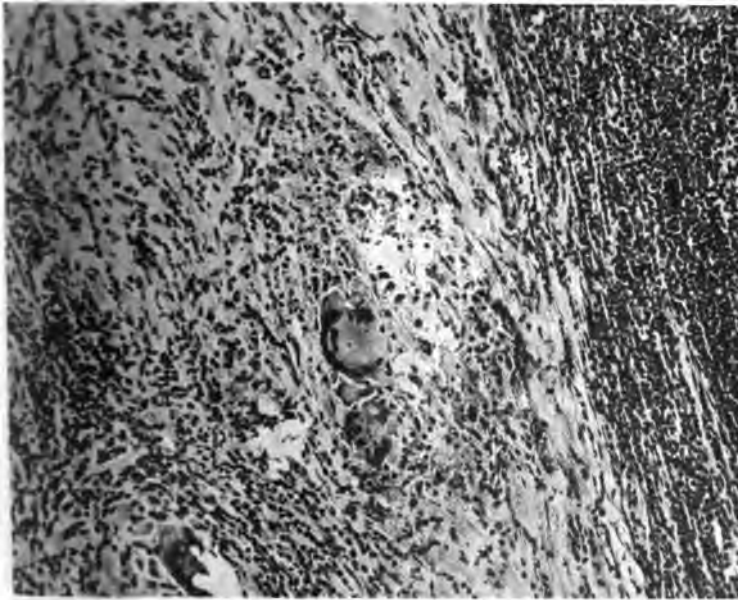
Fig. 234.—Photomicrograph (×120, Unna-Pappenheim stain) showing structures which may be either tuberculous giant-cells or atrophic nuclei.

TUBERCULOSIS OF THE BREAST

Office Number	Sex	Age	Tuberculous Heredity	Tuberculous Lesions in Other Organs	General Health	Type of Lesion	Number of Lesions	Side Involved	Quadrant of Location	Nipple	Skin	Enlargement of Axillary Glands Rt.	Enlargement of Axillary Glands Lt.	Enlargement of Cervical Glands Lt.	Enlargement of Cervical Glands Rt.	Breast Pain	Pathology	Koch's Bacilli in the Histologic Sections
4,522	M	52	–	++ lungs; left empyema	Poor	Abscess	Single	Lt.	Lower	–	Slight inflammation	–	–	–	–	+	Tuberculosis	
7,475	F	28	+	Lungs	Poor	Nodular	Single	Lt.	Upper exterior	–	–	–	–	–	–	Slight	Tuberculosis	
8,102	F	23	+	Lungs	Poor	Abscess	Single	Lt.	Lower exterior	–	Slight inflammation	–	–	–	–	Slight	Tuberculosis	
2,259	F	27	+	Lungs	Poor	Nodular	Mult.	Lt.	Upper exterior	–	–	–	+	–	–	Slight	Tuberculosis of breast	
6,353	F	40	–	–	Good	Nodular	Single	Rt.	Upper exterior	Retracted	–	–	–	–	–	Slight	Tuberculosis of breast	
9,700	F	28	–	Lungs	Poor	Nodular	Mult.	Lt.	Upper exterior	–	–	+	–	+	+	Slight	Tuberculosis of breast and glands	
9,700	F	26	–	Lungs	Poor	Nodular	Mult.	Rt.	Upper exterior and interior	–	–	–	–	–	–	Slight	Tuberculosis of breast	
17,117	F	22	–	–	Good	Cyst	Single	Lt.	Nipple region	–	–	–	–	+	+	Slight	Tuberculous wall of cyst	+
21,077	F	41	–	–	Good	Fistula	Single	Lt.	Upper exterior	–	Ulcerated	+	–	–	–	Slight	Tuberculous mastitis	
52,798	F	28	–	–	Excellent	Diffuse sclerosis	Single	Rt.	Generalized	Retracted	–	+	–	–	–	Slight	Tuberculous mastitis; tuberculous glands	+
68,625	F	42	–	Right adnexa and appendix removed elsewhere two years before	Poor	Diffuse sclerosis	Single	Rt.	Generalized	–	–	+	–	–	–	Slight	Tuberculosis of breast and glands	+

bloody discoloration of fat, cysts, fibrosis, lymphocytic infiltration, localized areas of caseation, and giant-cells.

A microscopic diagnosis is essential in practically all cases. This frequently must be aided by the demonstration of the Bacillus tuberculosis in smears, cultures, tissues, or by injection into guinea-pigs. The histologic diagnosis is often difficult or impossible because disintegrating atrophic acini, when surrounded by necrosis and fibrosis, sometimes resemble giant-cells. Mistakes are, therefore, not infrequent.

A correct diagnosis from a histologic standpoint can be made only when typical tubercles, with caseation, epithelioid cells, and giant-cells with peripheral nuclei, are present.

REFERENCES

1. Durante, L.: "Contributo clinico e anatomo-patologico allo studio della tubercolosi della mammella muliebre," Policlinico, 1914, xxi, Sez chir., 319–335.
2. Deaver, J. B.: "Tuberculosis of the Breast," Amer. Jour. Med. Sci., 1914, cxlvii, 157–185.
3. Leriche: "Tuberculose inflammatoire et maladie kystique du sein," Lyon méd., 1914, cxxii, 1076.
4. Pirrung, J. E.: "Tubercle of the Mammary Gland Simulating Cancer," Lancet-Clinic, 1914, cxi, 563.
5. Roffo, A. H., and Landivar, A. F.: "A propósito del origen linfático de la tuberculosis mamaria," Prensa méd. argentina, 1914, i, 33–37.
6. Miles, A.: "Notes on a Series of Cases of Tuberculosis of the Mamma," Edinburgh Med. Jour., 1915, xiv, 205–209.
7. Klose, H.: "Tuberkulose und Neubildung. I. Tuberkulose mit Adenocarcinom der Brustdrüse," Beitr. z. klin. Chir., 1910, lxvi, 1–7.
8. Duret, H.: "Tuberculose mammaire et adénite axillaire," Progrès méd., 1882, x, 157.
9. Verneuil: Quoted by Deaver, loc. cit.
10. Berchtold, E.: Ueber Mammatuberkulose, Uster, Weidenmann, 1890, 71 p.
11. Salomóni, A.: "Tubercolosi e tumori condromatosi della mammella," Clin. chir., 1901, ix, 169–178; 251–257.
12. Caminiti, R.: "Sulla tubercolosi primitiva della mammella," Riforma med., 1903, xix, 869–905.
13. Scott, S. R.: "Tuberculosis of the Female Breast," St. Bartholomew's Hosp. Rep., 1905, xl, 97–123.
14. Schmidt, E.: Ein Fall von Tuberculosis mammæ, Lübeck, Schmidt, 1905, 24 p.
15. Duvergey: "Tuberculose mammaire par voie lymphatique rétrograde à la suite d'une plaie infectée de la main," Jour. de méd. de Bordeaux, 1911, xli, 841.
16. Vignard and Pasquier: "Tuberculose du sein par infection ascendante? (Point de départ: tuberculose osseuse du pouce)," Gaz. méd. de Nantés, 1912, 2s., xxx, 493.
17. Putzu, F.: "Contributo allo studio della tubercolosi della mammella," Arch. internat. de chir., 1912–1913, vi, 222.
18. Bahuand: "Tuberculose du sein," Gaz. méd. de Nantés, 1906, xxiv, 317–319.
19. Braendle, E.: "Tuberkulose der Brustdrüse und die Dauerresultate ihrer operativen Behandlung," Beitr. z. klin. Chir., 1906, l, 215–228.
20. Cignozzi, O.: "Amputazione della mammella col metodo Tansini per tubercolosi," Policlin., 1910, xvii, sez. prat., 811–813.
21. Bloodgood: In Kelly, H. A., and Noble, C. P.: "Gynæcology and Abdominal Surgery," Phila., Saunders, 1907, vol. 2.
22. MacCarty, W. C.: "Histogenesis of Cancer of the Breast and Its Clinical Significance," Surg., Gynec. and Obst., 1912, xvii, 441–459.

STUDIES IN CLINICOPATHOLOGIC STANDARD-
IZATION AND EFFICIENCY *

WM. CARPENTER MacCARTY AND ALBERT COMPTON BRODERS

— ——

I. THE ACTUAL ERROR IN THE DIAGNOSIS OF MAMMARY CONDITIONS

A comparative examination of the clinical and pathologic diagnoses in the following series of 1800 mammary pathologic conditions operated on in the Mayo Clinic reveals certain items in medical efficiency of value from several standpoints.

The actual error consists of a clinical diagnosis of a malignant condition when a benign condition really exists, or vice versa. In these errors the indicated operation would be either too radical or not radical enough; the patient would be a victim of too little or too much surgery. Such actual error, from a clinical diagnostic standpoint, is certainly inevitable and unavoidable from the nature of the pathologic conditions involved, especially since it is a physical impossibility always to differentiate benign from malignant conditions by any known clinical methods. The nature of certain advanced pathologic conditions in the breast is very evident to the experienced clinician, but that there are conditions the diagnoses of which are certainly not evident is clearly revealed in the table presented on page 477. These uncertain conditions are apparently more numerous than the ordinary professional impression seems to convey.

Legitimate as the error is from the standpoint of the insufficiency of signs, symptoms, and clinical history, it is absolutely illegitimate when viewed from the standpoint of surgical pathologists who, unfortunately, are painfully inadequate in quality and quantity in the hospitals of this and other countries.

In the past this inadequacy was unavoidable on account of a lack of

CLINICAL DIAGNOSES	PATHOLOGIC DIAGNOSES					
	Carci-noma	Fibro-adenoma	Intracan-alicular Fibro-adenoma	Chronic Mastitis	Cyst	Total
Carcinoma................	722	7	0	27	7	763
Epithelioma..............	2	0	0	0	0	2
Carcinoma?..............	90	12	0	38	17	157
Sarcoma?................	3	0	0	1	0	4
Sarcoma.................	1	1	0	0	1	3
Adenoma................	10	34	10	25	9	88
Fibro-adenoma	5	58	9	3	4	79
Intracanalicular fibroma....	0	0	3	0	0	3
Fibroma.................	0	10	10	4	0	24
Cystadenoma.............	0	3	1	1	0	5
Tumor..................	44	83	31	88	49	295
Benign..................	6	15	0	5	4	30
Benign?.................	2	0	0	2	2	6
Nodules.................	1	3	1	3	0	8
Cyst....................	6	9	0	10	12	37
Cyst?...................	0	0	0	0	3	3
Chronic mastitis..........	9	24	10	139	8	190
Chronic mastitis?..........	1	0	0	3	0	4
Papilloma...............	0	0	0	1	0	1
Ulcer...................	1	0	0	0	0	1
Tuberculosis.............	2	0	0	0	0	2
Abscess.................	2	0	0	0	0	2
Myxoma.................	0	0	0	0	1	1
No diagnosis.............	26	35	1	26	4	92
Total.................	933	294	76	376	121	1800

The above table presents the following detailed facts:

PERCENTAGE OF ACTUAL ERROR

Total No. of mammary carcinomas diagnosed in the surgical laboratory, 933

" " " mammary carcinomas diagnosed benign by the clinician   41= 4 per cent.

" " " clinical diagnoses of carcinoma in series...............   763

" " " clinical diagnoses of carcinoma which were incorrect....   41= 5   "

" " " chronic mastitides diagnosed in the surgical laboratory   376

" " " chronic mastitides diagnosed a malignant condition by the clinician....................................   28= 7   "

" " " clinical diagnoses of chronic mastitis which were incorrect...   51=26   "

" " " clinical diagnoses of chronic mastitis which were carcinoma...   9= 4   "

" " " fibro-epithelial neoplasms diagnosed in surgical laboratory...   370

" " " fibro-epithelial neoplasms diagnosed a malignant condition by the clinician.............................   8= 2   "

" " " clinical diagnoses of fibro-epithelial neoplasm..........   200

" " " clinical diagnoses of fibro-epithelial neoplasms which were a malignant condition.......................   15= 7   "

" " " cysts diagnosed in the surgical laboratory.............   121

" " " cysts diagnosed carcinoma or sarcoma by the clinician.   8= 6   "

" " " clinical diagnoses of cyst............................   37

" " " clinical diagnoses of cyst which were carcinoma........   6=16   "

" " " clinical diagnoses of adenoma........................   88

" " " clinical diagnoses of adenoma which were carcinoma....   10=11   "

" " " clinical diagnoses of fibro-adenoma..................   79

" " " clinical diagnoses of fibro-adenoma which were carcinoma   5= 6   "

" " " clinical diagnoses of benign.........................   30

" " " clinical diagnoses of benign which were carcinoma......   6=20   "

operative surgery in early pathologic conditions, the small number of pathologists to study early malignant conditions in association with inflammatory lesions, and the scarcity of pathologists as a result of the rush of laboratory men into the fields of immunology, serology, and bacteriology, and, lastly, the inadequacy of monetary and moral compensation sufficiently large to allow constructive, energetic men of vision to spend their lives in this branch of medicine.

Recent years have somewhat altered these circumstances. Surgeons by their own initiative and perfection of surgical technic have opened a new field for the pathologist who happens to be especially interested in the immediate clinical aspect of efficiency in therapeutics and fresh tissue research. This field presents methods which give to the surgeon during operations the same type of service which range-finders give artillerymen in battle. During operative procedure accurate gross and microscopic diagnoses may be given to the operator in from fifteen seconds to three minutes, during which time no operation can be completed and no extra material risk is added to the duration of the anesthesia.

In one organ alone, i. e., the breast, efficiency may be seen in an item which in itself is positive proof of the valuable service rendered by the modern fresh-tissue surgical pathologist. This consists of the fact that of 933 mammary carcinomas, the pathologist discovered, during operation, 211 (22 per cent.) carcinomas which the clinician and surgeon had diagnosed benign conditions or in which they did not make a positive diagnosis. Positively recorded clinical diagnoses only are included in this number.

The practical surgeon nowadays, however, is beginning to learn that clinical diagnoses in the breast are frequently not positive. When the surgical pathologist picks up 22 per cent. of the total mammary carcinomas by means of his special training and methods, he renders a service of supreme value not only to the surgeon, but to the patient.

The question which arises from these facts is: Can surgical work be done on this organ efficiently and justly without such assistance? The answer is evident in the figures presented herein, and one strongly suspects that what has been termed legitimate error becomes illegitimate error without such assistance. This statement may appear too radical in view of the fact that a sufficient number of men especially trained in surgical pathologic diagnosis is not available to supply all hospitals. However, this does not alter the truth relative to surgical and clinical

efficiency.   An extensive and wordy dissertation on this question could not emphasize the truth to this greater advantage than the figures themselves.

II. THE APPARENT ERROR IN THE DIAGNOSIS OF MAMMARY CONDITIONS

In the first study it was pointed out that while there is a definite clinical error dependent on inadequacy of clinical methods, this legitimate error becomes illegitimate from the standpoint of justice to the patient simply because such error might be avoided by the utilization of properly trained surgical pathologists in immediate conjunction with operative procedure.

While the apparent error is not of such serious moment to the patient, it occurs in a much higher percentage of clinical diagnoses than does the actual error.   It consists of calling a benign condition by the name of another benign condition or a malignant condition by the name of some other malignant condition.   In neither case would the error in nomenclature change the operative procedure, and, therefore, would not cause the patient to undergo any unnecessary radical or insufficient treatment.

It is of interest and importance only from the standpoint of efficiency of nomenclature in the transference of thought from one scientific person to another.

Any business or military code with an error of from 8 to 50 per cent. would not be tolerated, and still the medical profession, which is striving for scientific efficiency, utilizes such a code.   The following figures represent the facts for one organ, i. e., the mammary gland:

Total No. of chronic mastitides diagnosed in the surgical laboratory	376	
" " " chronic mastitides diagnosed fibro-epithelial neoplasms	33 =	8 per cent.
" " " clinical diagnoses of chronic mastitis...............	190	
" " " clinical diagnoses of chronic mastitis which were fibro-epithelial neoplasms............................	34 = 17	"
" " " fibro-epithelial neoplasms diagnosed in the surgical laboratory...	370	
" " " fibro-epithelial neoplasms diagnosed chronic mastitis...	34 = 9	"
" " " fibro-epithelial neoplasms diagnosed some other benign condition...	32 = 8	'
" " " cysts diagnosed in the surgical laboratory...........	121	
" " " cysts diagnosed fibro-epithelial neoplasms...........	14 = 11	"
" " " clinical diagnoses of cyst..........................	37	
" " " clinical diagnoses of cyst which were fibro-epithelial neoplasms..	9 = 24	"
" " " clinical diagnoses of cyst which were chronic mastitis...	10 = 27	"
" " " clinical diagnoses of adenoma......................	88	
" " " clinical diagnoses of adenoma which were chronic mastitis	25 = 25	"
" " " clinical diagnoses of adenoma which were fibro-epithelial neoplasms..	44 = 50	"

In this series the following nomenclature was utilized by the clinicians:

Adenoma.
Adenofibroma.
Lipoma.
Benign.
Cyst.
Carcinoma.
Chronic mastitis.
Cystic fibro-adenoma.
Cystadenoma.
Cystic degeneration.
Fibroma.
Fibro-adenoma.
Sarcoma.
Fibromyxoma.

Growth.
Lipoma.
Lump.
Myxoma.
Mass.
Malignant.
Nodule.
Neuroma.
No diagnosis.
Papilloma.
Plaque.
Retention cyst.
Sebaceous cyst.

These names were applied to the following pathologic conditions:

Adenofibroma.
Adenoma.
* Adenomyxofibroma.
* Angioma.
* Adenofibromyxoma.
* Adenomyxoma.
Benign.
Cyst.
* Cystic fibroma.
Cystadenoma.
* Chondrolipofibroma.
Cystic fibro-adenoma.
Cystic adenofibroma.
* Calcareous tumor.
Chronic mastitis.
* Cystic intracanalicular papillary adeno-
     fibroma.
* Calcareous adenoma.
* Cystic calcareous fibroma.
* Calcareous intracanalicular adeno-
     fibroma.
Carcinoma.
* Dermoid.
* Embryoma.
Fibro-adenoma.
Fibroma.
Fibromyxoma.

* Fibrolipoma.
* Fibromyoma.
* Fibrocystadenoma.
* Fibromyxo-adenoma.
* Intracanalicular myxoma.
* Intracanalicular fibroma.
* Intracanalicular fibro-adenoma.
* Intracanalicular adenofibroma.
* Intracanalicular papilloma.
* Intracanalicular fibromyxoma.
* Intracystic papilloma.
* Intracanalicular myxofibroma.
* Intraductal papilloma.
* Intracanalicular adenomyxoma.
* Intracanalicular fibro-adenomyxoma.
* Intracanalicular papilloma (malignant).
Lipoma.
* Myxofibroma.
* Myxofibro-adenoma.
Myxoma.
* Myxo-adenofibroma.
* Papillary cyst.
* Papillary fibro-adenoma.
* Papillary fibrocystadenoma.
* Pericanalicular fibroma.
Sebaceous cyst.

In utilizing this nomenclature the following errors were made:

PATHOLOGIC DIAGNOSIS		CLINICAL DIAGNOSIS
Diffuse lipoma	called	chronic mastitis.
Cyst	"	fibro-adenoma.
Fibro-adenoma	"	adenoma.
Fibro-myxoma	"	carcinoma.
Adenofibroma	"	fibro-adenoma.
Fibro-adenoma	"	retention cyst.
Fibro-adenoma	"	adenofibroma.
Adenofibroma	"	carcinoma.
Fibro-adenoma	"	fibroma.

* Pathologic terms not utilized by the clinicians.

Pathologic Diagnosis		Clinical Diagnosis
Cystic fibro-adenoma	called	myxoma.
Adenofibroma	"	chronic mastitis.
Cystic fibro-adenoma	"	chronic mastitis.
Cysts	"	carcinoma.
Cysts	"	chronic mastitis.
Fibro-adenoma	"	chronic mastitis.
Intracanalicular fibroma	"	carcinoma.
Lipoma	"	cyst.
Papillary fibrocystadenoma	"	cystadenoma.
Cyst	"	adenoma (early carcinoma).
Fibro-adenoma	"	cystadenoma.
Cystadenoma	"	adenoma.
Adenofibroma	"	fibroma.
Intracanalicular papilloma	"	chronic mastitis.
Intracanalicular fibro-adenoma	"	fibroma.
Fibrolipoma	"	chronic mastitis.
Intracanalicular fibro-adenoma	"	adenoma.
Adenofibroma	"	cystadenoma.
Fibrocystadenoma	"	adenoma.
Intracanalicular fibro-adenoma	"	fibro-adenoma.
Intracanalicular fibro-adenoma	"	chronic mastitis.
Myxoma	"	neuroma.
Intracanalicular adenofibroma	"	fibroma.
Cyst	"	adenoma.
Adenomyxoma	"	adenoma.
Lipoma	"	fibroma.

These facts, vivid as they are, mean something to an analytic mind which is dealing with scientific efficiency, and from them the following generalization may be logically made: The medical profession is trying to adapt detailed pathologic nomenclature and terminology to conditions which do not always reveal their detailed characteristics through signs and symptoms. This usage on the part of clinicians has been the logical outcome of the natural evolution of our knowledge of medicine, but the evolution should not stop at this stage. Efficiency demands, at least, an attempt at correction.

Experience with this series of cases has taught that the clinicians and surgeons really desire certain fundamental facts insofar as the patient is concerned. They want to know whether the condition is benign or malignant, and whether it is operable or inoperable. These are the essential factors which the practical surgical pathologist must face with his colleagues, the clinicians and surgeons. Detailed names play a very small rôle in the rendition of his assistance in such conditions.

It has been urged by surgeons who have had some training in pathology that they should be able to make their own gross diagnoses. This is ideal and possible if surgeons would spend time enough in learning pathology. Six months, a year, or five years of training in gross pathology will not keep a surgeon from making a high percentage of error in

'16—31

gross diagnoses. It must be fully realized by the medical profession that in many conditions a microscopic diagnosis is absolutely necessary. This requires special training and experience far beyond that which can be obtained in the regular medical course or during internship in a laboratory, or perhaps a course abroad.

Nomenclature and classifications which have been made by excellent surgeons who were poor pathologists have been largely responsible for much of the chaos in clinical pathology. Synonyms and classifications are almost as numerous as text-books. There are apparently no signs, symptoms, and clinical histories which will positively differentiate any of the following conditions: adenoma, adenofibroma, cystic fibro-adenoma, cystadenoma, fibroma, fibro-adenoma, myxoma, lipochondrofibroma, and fibromyxoma. And still the clinicians and surgeons continue to utilize such terms in spite of their cognizance that the clinical differential diagnosis is impossible by any known methods.

The clinicians in this series of cases have automatically shown evidence of the inefficiency of such usage, and have substituted in their practice, during recent years, the terms benign, tumor, growth, lump, nodule, and mass. To them these terms are practically synonymous and do not describe a detailed microscopic condition which they cannot see. This is a hopeful sign for scientific efficiency in medicine.

In this series of cases the clinicians refrained from using such terms as:

$$
\text{Intracanalicular} \begin{cases} \text{myxoma.} \\ \text{fibroma.} \\ \text{fibro-adenoma.} \\ \text{adenofibroma.} \\ \text{papilloma.} \\ \text{fibromyxoma.} \\ \text{adenomyxoma.} \end{cases}
$$

These neoplasms, however, form a group which constitutes a much higher percentage of benign solid tumors of the breast than do the fibromas, adenomas, adenofibromas, fibro-adenomas, cystadenomas, myxomas, and fibromyxomas, terms with which the clinician is perhaps much more familiar.

The percentage of error in terminology is greatest in the group of benign conditions. From a standpoint of clinical efficiency these mistakes represent only an apparent error, and certainly do not reflect on the clinician's ability to render scientific service to his patients.

The names sound well, but what is needed and demanded today is clear, concise, accurate, and simple scientific medical practice which can

be expressed in a clear, concise, accurate, and simple scientific clinico-
pathologic terminology and nomenclature.

III. THE AVOIDED ERROR IN THE DIAGNOSIS OF MAMMARY CONDITIONS

The third type of error in this series has been called the "avoided
error," which means that error did not occur simply because the clinician
utilized some doubtful or non-specific nomenclature, such as carcinoma?
benign? malignant? chronic mastitis? cyst? sarcoma? tumor, nodule,
growth, mass, and no diagnosis, and left the actual diagnosis for the
surgical pathologist to make.

The frequency of such a clinical habit may be seen in the following
percentages:

Total No. of mammary carcinomas diagnosed in the surgical labora-
tory... 933
"   "   " mammary carcinomas diagnosed a possible malignant
condition... 96 = 10 per cent.
"   "   " clinical diagnoses of carcinoma?...................... 157
"   "   " clinical diagnoses of carcinoma? which were benign..... 67 = 42   "
"   "   " clinical diagnoses of carcinoma? which were malignant.. 90 = 57   "
"   "   " chronic mastitides diagnosed in the surgical laboratory.. 376
"   "   " chronic mastitides diagnosed a possible malignant con-
dition.. 44 = 11   "
"   "   " chronic mastitides diagnosed "no diagnosis".......... 26 = 6   "
"   "   " chronic mastitides diagnosed "tumor"............... 88 = 23   "
"   "   " chronic mastitides diagnosed as possible malignant con-
dition, tumor, nodule, or no diagnosis.............. 161 = 42   "
"   "   " fibro-epithelial neoplasms diagnosed in the surgical labor-
atory.. 370
"   "   " fibro-epithelial neoplasms diagnosed a possible malignant
condition... 12 = 3   "
"   "   " fibro-epithelial neoplasms diagnosed "no diagnosis".... 36 = 9   "
"   "   " fibro-epithelial neoplasms diagnosed "tumor"......... 114 = 30   "
"   "   " cysts diagnosed in the surgical laboratory............ 121
"   "   " cysts diagnosed "tumor"........................... 49 = 40   "
"   "   " cysts diagnosed carcinoma?......................... 17 = 14   "
"   "   " cysts diagnosed benign?.............................   2 = 1   "
"   "   " cysts diagnosed "no diagnosis".....................   4 = 3   "
"   "   " clinical diagnoses of "tumor"....................... 295
"   "   " clinical diagnoses of "tumor" which were a malignant
condition... 44 = 14   "
"   "   " clinical diagnoses of "tumor" which were a benign con-
dition.. 251 = 86   "

Perhaps the most interesting feature in this group of errors is the
fact that 42 per cent. of the clinical diagnoses of "carcinoma?" were
actually benign.

Another interesting and important feature is the apparent realiza-
tion on the part of the clinician that absolute diagnoses in the breast are
not possible in a great many cases. This realization may be seen in the

frequency of avoided errors, which consist of "carcinomas?" 157, "sarcoma?" 4, "tumor" 295, "benign?" 6, "nodule" 8, "cyst?" 3, "chronic mastitis?" 4, and "no diagnosis" 92, a total of 569, or 31 per cent. of all diagnoses. These figures certainly show a simple truth, *i. e.*, that the present pathologic nomenclature is quite inefficient from a clinical standpoint, and suggests the necessity of a more adequate nomenclature.

IV. CLINICOPATHOLOGIC NOMENCLATURE OF MAMMARY CONDITIONS

In the first three studies it has been clearly shown that an analysis of 1800 mammary pathologic conditions from the comparative standpoint of clinical and pathologic diagnoses reveals certain diagnostic errors which prove at least three definite things:

1. An actual error of from 2 to 26 per cent.
2. An apparent error of from 8 to 50 per cent.
3. An avoided error of from 1 to 86 per cent.

Coincidentally with the determination of these percentages it was shown that 31 per cent. of the clinical diagnoses of mammary conditions were made with a full recognition on the part of the clinician of the fact that a positive diagnosis could not be made. It was also shown that the actual or so-called legitimate error becomes an illegitimate error if not checked during operations by the immediate services of a well-trained surgical pathologist.

The apparent and avoided errors signified one essential fact, *i. e.*, that the present pathologic nomenclature is inadequate, inefficient, and unscientific when utilized for clinical diagnosis.

In view of this and of the necessity for greater efficiency, a simple clinicopathologic nomenclature has been utilized successfully by the writers.

For the sake of convenience all pathologic conditions in the breast may be divided into encapsulated and non-encapsulated (diffuse) conditions, the history of which is dependent on the reaction of the component tissues of the breast, regardless of the irritative or destructive agencies.

It has been shown in the breast and other organs that the aggregations of specialized and differentiated cells which we call "tissues" react to irritation in certain ways. Under certain conditions the tissue-cells are rapidly or gradually destroyed, and there is a successful or unsuccessful attempt on the part of nature at their replacement or regenera-

tion. The success of this attempt means healing, and the unsuccessful gradual attempt is associated with the following histologic pictures, dependent on the quality, quantity, and duration of action of the destructive agent or agents:

1. Primary cytoplasia, when the differentiated tissue-cells are present, plus a hypertrophy of the regenerative cells of the tissues.

2. Secondary cytoplasia, when the differentiated cells have partially or completely disappeared, plus a hyperplasia of the regenerative cells.

3. Tertiary cytoplasia, when the hyperplastic regenerative cells have migrated into the surrounding stroma.[4]

An unsuccessful attempt at replacement and regeneration in the presence of any acute virulent destruction, such as pyogenic infections, results in abscess or necrosis and destruction of the whole organism. An unsuccessful attempt at replacement and regeneration in the presence of chronic non-virulent tissue-destruction results in a neoplastic hyperplasia of the regenerative cells of one or more of the tissues, without their complete differentiation into tissues or the eventual destruction of the whole organism. It is this neoplastic hyperplasia, with or without subsequent differentiation into tissues, which is of importance in chronic mastitis and benign and malignant new-growths.

It is self-evident that a new-growth of cells, benign or malignant, must grow from something, and that the cells of any tissue capable of growth are the regenerative cells. In the epithelial tissue of the breast these lie between the columnar or cuboid secretory cells and the stroma. In the connective tissue the regenerative cells are the fibroblasts. In the presence of a chronic destruction of either or both of these special tissues there is a hypertrophy of the regenerative cells. This hypertrophy is often associated with or followed by hyperplasia and sometimes by migration.

In the condition of hypertrophy there is no evidence which warrants a suggestion of clinical malignancy because practically all chronic mastitides present this picture, and every clinician and pathologist knows that all chronic mastitides are not associated with either benign or malignant neoplasms.

In the condition of hyperplasia of the regenerative cells the problem of malignancy or benignancy becomes more difficult because the hyperplastic regenerative cells are frequently morphologically identical with malignant cells, but are still within the normal bounds of their specific tissues.[5]

Who is there who has the power to say whether these growing cells will be brought back to their normal power of differentiation by means of normal tissue control, or continue to grow and migrate into neighboring and distant tissues and becomes malignant?

Insofar as the clinician, pathologist, and patient are concerned, this is an indeterminate condition which definitely forms a histologic line of demarcation between that which is definitely benign and that which is malignant.

The biologic history of the evolution of these regenerative cells may be shown in the accompanying diagram, in which there is represented segmentation of the fertilized ovum and the production of cells which either produce, immediately, the tissues or the regenerative cells which later become differentiated into tissues. When the cells that are produced in this stage of prodifferentiation become differentiated in the normal course of embryologic development, normal tissues and a normal organism result.

It has been shown that in adult life the regenerative cells which occur in the stage of prodifferentiation in the postnatal organism sometimes become hyperplastic (secondary cytoplasia); that they produce new-growths in which the tissues are differentiated, and that they sometimes produce new-growths which consist of undifferentiated migratory cells. The new-growths with differentiation constitute the benign neoplasms. The new-growths with migration constitute the malignant neoplasms.

Fertilization of the ovum
↓
Segmentation
↓
Prodifferentiation (pro-tissue cells and regenerative cells).

Differentiation (into specific cells).   Neoplasia (undifferentiated).

Differentiation (benign neoplasms).   Migration (malignant neoplasms).

Differentiation (incomplete).   Undifferentiation.
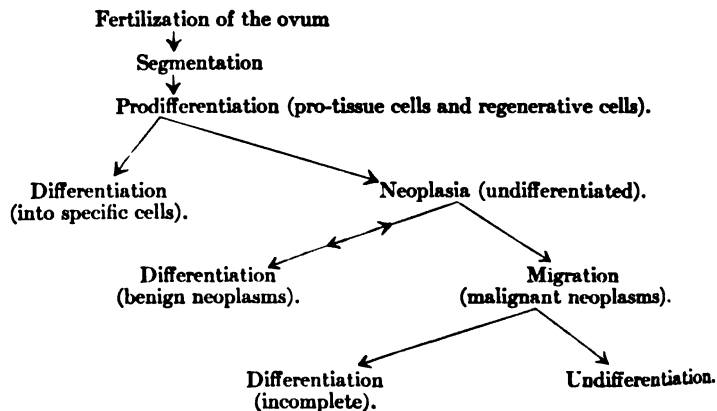
These facts are true not only of epithelial tissue, but also of connective or fibrous tissue and perhaps all tissues. In benign fibro-epithelial

neoplasms the condition of secondary and tertiary cytoplasia also some-times occurs, hence the presence of malignant conditions arising in the so-called fibro-epithelial neoplasms, which are usually benign. In so far as the reaction of the tissues of the breast is concerned, it matters not whether they are encapsulated or non-encapsulated—they react in these three degrees to chronic destruction. Upon the degree of reaction will depend the life history of the breast, and consequently the whole body, of which the breast is a part. Biologically in these three stages we have cellular destruction, cellular hypertrophy, cellular hyperplasia, and cellular migration.

The regenerative cells possess certain possibilities. They produce specialized differentiated tissue-cells, they reproduce themselves as un-differentiated cells, and they migrate as undifferentiated cells. From a clinical standpoint in the condition of hypertrophy they are carrying out a normal communistic existence, i. e., producing a special tissue which is to work in conjunction with other special tissues of the multi-cellular organism. In the second condition they produce an indeter-minate condition, the end result of which cannot be prophesied by any known methods. In the third condition experience has taught us that the cells, when they are in the stroma, continue their migration even to distant organs, grow, and eventually destroy the life of the organism.

Regardless of whether we call a chronic inflammatory mammary condition chronic mastitis, and benign tumors, e. g., adenomas, fibromas, adenofibromas, fibro-adenomas, fibromyxomas, myxofibromas, myxo-mas, or intracanalicular fibro-adenomas, adenofibromas, myxomas, adenomyxomas, or any other names which have been given to the va-rious conditions, or whether we call a condition Schimmelbusch's dis-ease, Reclus' disease, abnormal involution, senile parenchymatous hy-pertrophy, or any other of the ten or twelve synonyms, or whether we call carcinoma scirrhus, adenocarcinoma comedocarcinoma, or carci-noma simplex, or any other name, the fact relative to the conditions which are present remains simply one of reaction on the part of the cells involved, and so far as the clinical, surgical, and pathologic experience of the writers has been concerned, the patient's welfare depends abso-lutely on deciding whether the cytologic activity is benign, indeter-minate, or malignant. The names of tumors play no great rôle. The nomenclature in text-books does not produce a clear conception of what actually exists from the clinical standpoint. It is true that neoplasms are grouped in text-books into benign and malignant, and under each

group there is a long list of names of conditions which have been described in detail from the pathologist's standpoint. That this detailed description, with its nomenclature, has been of great efficiency to the clinician may be answered in the negative from our experience. A glance at the percentages of error which have been made during the utilization of, and on account of, the present text-book nomenclature is sufficient to support the statements made above.

In summarizing the writers' solution of this problem it may be stated that the main object is the proper treatment of the patient, which may be best accomplished by a simple realization of the fundamental facts that the history of the breast is the history of its tissues in their battle against irritants and destructive agencies of any kind, and that all tissue-cells react in certain ways to these agencies, depending on the quality, quantity, and duration of action. The histologic pictures of this reaction represent tissue destruction, tissue replacement, cellular regeneration, cellular neoplasia, and cellular migration.

Clinical experience has taught that destruction of tissue-cells may be complete and fatal to the organism, or it may be incomplete and the destroyed tissues be replaced or regenerated. It may be incomplete and still great enough to prevent complete replacement or regeneration during which a new-growth (neoplasia) occurs, the cells of which may become differentiated and are benign, or migrate and are malignant. These are the clinical effects of reaction, and it is these simple effects which should be borne in mind by the clinician, surgeon, and pathologist, regardless of the name of the tumor.

The conditions of the tissues are really what the clinician desires. From this, by correlation with clinical experience, he may decide on the benignancy or malignancy, the degree of treatment, and the future of the patient.

It may be definitely stated by a pathologist familiar with the stages of tissue reaction that there are primary, secondary, and tertiary cytoplasia, which have three definite clinical meanings, regardless of names of tumors which do not always have definite clinical value. If the clinician or surgeon desires still to group conditions into encapsulated and non-encapsulated, he is dealing with:

$$\left.\begin{array}{c}\text{Encapsulated} \\ \text{or} \\ \text{Non-encapsulated}\end{array}\right\} \left.\begin{array}{c}\text{Primary,} \\ \text{Secondary,} \\ \text{or} \\ \text{Tertiary}\end{array}\right\} \text{Cytoplasia.}$$

His error then becomes dependent simply on his ability to determine by signs, symptoms, and clinical history whether he thinks a condition is benign, malignant, or doubtful. The tissue involved and the degree of involvement can be decided only by the surgical pathologist, and this decision can be made during operations without added injury to the patient provided the lesion is excised instead of incised.

At this juncture clinicians will doubtless say that there are so many cases which are quite evident. True as this is, there still remains a 5 per cent. error in the diagnoses of carcinoma and a failure to discover positively 22 per cent. of carcinomas. These percentages demand the immediate service of the laboratory. If the plan set forth in this series of papers be adhered to, the 5 per cent. and 22 per cent. will be done away with; the apparent error of 8 to 50 per cent. will completely disappear, and such non-descriptive and unscientific terms as mass, tumor, nodule, and growth, and names of tumors with question marks, will not be necessary in clinical diagnoses.

The medical code for pathologic conditions in the breast will be transformed from one of inefficiency to one of scientific efficiency, and the patient will reap the benefit.

REFERENCES

MacCarty, W. C.: "Carcinoma of the Breast," Tr. South. Surg. and Gynec. Assoc., 1910, xxiii, 262–270.

"The Histogenesis of Cancer of the Breast," Surg., Gynec. and Obst., 1913, xvi, 441–459.

"Clinical Suggestions Based Upon a Study of Primary, Secondary (Carcinoma?) and Tertiary or Migratory (Carcinoma) Epithelial Hyperplasia in the Breast," Surg., Gynec. and Obst., 1914, xviii, 284–289.

"Studies in the Etiology of Cancer. Study I. Precancerous Conditions," Jour. Iowa State Med. Soc., 1914, iv, 1–11.

"Studies in the Etiology of Cancer. Study II. Histogenesis of Cancer of the Stomach," Amer. Jour. Med. Sci., 1915, cxlix, 469–476.

"Studies in the Etiology of Cancer. Study III. The Biologic Position of the Cancer Cell," Pan-Amer. Surg. and Med. Jour., 1915, xx.

"Studies in the Etiology of Cancer. Study IV. Notes on the Regularity and Similarity of Cancer Cells," Collected Papers, Mayo Clinic, 1914, pp. 600–604.

"Studies in the Etiology of Cancer. Study VIII. The Evolution of Cancer," Collected Papers, Mayo Clinic, 1915, pp. 903–917.

"New Facts and Their Clinical Significance Concerning Cancer," Surg., Gynec. and Obst., 1915, xxi, 6–8.

"A New Classification of Neoplasms and Its Clinical Value," Amer. Jour. Med. Sci., 1916, cli, 799–806.

MacCarty, W. C., and Mensing, E. H.: "The Relation Between Chronic Mastitis and Cancer of the Breast," St. Paul Med. Jour., 1916, xviii, 164–167.

DUCTLESS GLANDS

TABLE 2.—THE EFFECT OF DECREASE IN TEMPERATURE ON A SERIES OF NORMAL AND OPERATED SPERMOPHILES

Date	Time Observed A.M.	Normal Adult Male	Normal Adult Female	Adult: Ovaries Removed	Adult: Ovaries Removed	Normal Adult Female	Normal Young Male	Normal Young Female	Adult: Testicles Removed	Young: Testicles Removed	Young: Testicles Removed	Young: Testicles Removed	Adult: Ovaries Removed	Room Temperature °C.
11-11-15	8.00	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	25°
11-12-15	8.00	Slightly torpid	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	20°
11-13-15	8.00	Torpid	Active	Active	Torpid	Torpid	Torpid	Active	Active	Slightly torpid	Active	Active	Slightly torpid	19°
11-14-15	9.00	Torpid	Slightly torpid	Slightly torpid	Torpid	Torpid	Torpid	Torpid	Slightly torpid	Active	Slightly torpid	Active	Torpid	18°
11-15-15	8.00	Torpid	Slightly torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Slightly torpid	Active	Active	Active	Torpid	17°
11-16-15	8.00	Torpid	Slightly torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Slightly torpid	Slightly torpid	Slightly torpid	Active	Torpid	16°
11-17-15	8.00	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Slightly torpid	Torpid	Slightly torpid	Active	Torpid	15°
11-18-15	8.00	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Active	Torpid	10°
11-19-15	8.00	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Active	Torpid	10°
11-20-15	8.00	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Slightly torpid	Torpid	5°

Date	Time Observed A.M.	Adult: Ovaries Removed	Adult: Ovaries Removed	Adult Female: Thyroid Removed	Adult Female: Thyroid Removed	Adult Female: Thyroid Removed	Adult Female: Thyroid Removed	Adult Female: Adrenals Removed	Adult Female: Adrenals Removed	Adult Female: Adrenals Removed	Adult Female: Adrenals Removed	Adult Female: Adrenals Removed	Adult Female: Adrenals Removed	Room Temperature °C.
11-11-15	8.00	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	25°
11-12-15	8.00	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	20°
11-13-15	8.00	Slightly torpid	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Slightly torpid	19°
11-14-15	9.00	Slightly torpid	Torpid	Slightly torpid	Slightly torpid	Slightly torpid	Active	Active	Active	Slightly torpid	Slightly torpid	Active	Slightly torpid	18°
11-15-15	8.00	Torpid	Torpid	Slightly torpid	Torpid	Slightly torpid	Active	Active	Active	Slightly torpid	Slightly torpid	Active	Slightly torpid	17°
11-16-15	8.00	Torpid	Torpid	Active	Torpid	Torpid	Torpid	Active	Active	Slightly torpid	Active	Active	Torpid	16°
11-17-15	8.00	Slightly torpid	Torpid	Active	Slightly torpid	Slightly torpid	Slightly torpid	Active	Active	Slightly torpid	Slightly torpid	Active	Torpid	15°
11-18-15	8.00	Torpid	Torpid	Torpid	Slightly torpid	Slightly torpid	Torpid	Active	Torpid	Slightly torpid	Torpid	Active slightly torpid	Torpid	10°
11 10-15	8.00	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	10°
11-20-15	8.00	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	Torpid	5°

The animals hibernated normally during the winter of 1914–15 and the fall of 1915. During the summer of 1915 the ovaries were removed from 12 animals. All hibernated under the same condition as the normal animals.

The Thyroids.—The histologic picture of the thyroid of the spermophile is uniform. The acini are relatively large and filled with colloid; the cells, low or flat. The secretion granules are usually few in number. I have not noticed any difference between the thyroids of active and hibernating animals.

The thyroid can be removed in the adult animal without the production of any changes. In July, 1914, the thyroids were removed from four spermophiles. These hibernated normally during the winter of 1914–15 and two were alive and hibernated during the fall of 1915. During the summer of 1915 the thyroids were removed from twelve animals. These hibernated under the same condition as the controls. In the animals operated on histologic examination showed that the thyroid was removed, although it was impossible to state that all thyroid tissue had been taken out. Necropsies were performed on practically all the animals and in only one was any thyroid tissue found on macroscopic examination.

The Parathyroids.—The parathyroids are relatively large in the spermophile. They are found not only attached to the thyroids, but also buried in the hibernating gland in the neck or anterior mediastinum. The histologic examination of these glands shows that in some animals they undergo very slight changes during hibernation. These changes consist in a decrease in their ability to take up the stains and a more irregular arrangement of the cells. In many hibernating animals they cannot be observed.

The Thymus.—A considerable amount of lymphoid tissue is always found buried in the substance of the hibernating gland in the anterior mediastinum. Hassall's corpuscles were noted in only a few of the animals examined. In some cases the staining ability of the lymphoid tissues and corpuscles of the gland from the hibernating animal seemed to be decreased. This decrease, however, was not uniform and so slight as not to warrant any positive statement.

The Islands of Langerhans.—The histologic picture of the pancreas of a hibernating spermophile does not differ essentially from that of a resting pancreas. The islands of Langerhans are large and well developed in the spermophile, and the A and B cells are well differentiated.

The only changes noted in the islands of the hibernating animal were a very slight decrease in staining properties and an irregularity in the arrangement of the cells. This change is not uniform.

The Adrenals.—The adrenal of the spermophile is a small but perfect gland having a medulla and cortex with its three fairly well-defined zones. This gland undergoes fairly definite and uniform seasonal changes. However, these changes have not been observed in all animals. The adrenal shows a gross increase in size in the spring and on histologic examination all the cells of both the cortex and medulla are found to be swollen. The main change takes place in a stratum of cells which are located in the inner part of the columns of the zona fasciculata. These cells are greatly swollen and very large in the spring. As the season advances the size of the adrenal decreases. Histologically all the cells appear to become smaller, but the major changes consist in a marked decrease in the cells of the inner portion of the zona fasciculata and a vacuolization of the cells of the zona granulosa and the upper portion of the zona fasciculata. During hibernation the latter changes seem to be accentuated but the lipoid content does not seem to change greatly. The medullary cells shrink very slightly during hibernation.

I was surprised to discover that the adrenals could be removed from the spermophile without producing immediate death, except in a small percentage of cases. In a few instances the animals died typical deaths from adrenal insufficiency. As a rule, the animal recovered from the operation and either became perfectly normal or more frequently lost weight and strength gradually, dying several weeks after removal of the last gland. In some cases necropsy revealed a hypertrophied accessory adrenal, but in most cases a diligent search with the bichromate method and histologic examination of suspicious particles did not reveal any adrenal tissue.* This probably does not mean that the spermophile can live without adrenal tissue or that another gland vicariously takes up its function, but that scattered bits of adrenal tissue which were too small to be found without serial section of the whole animal were enough to keep the animals alive for various lengths of time. However, it is of particular importance in the study that, at any event, the animal in which the adrenals were removed had a minimum amount of functionating adrenal tissue. This was amply proved by the fact that most of the animals became thin and weak and died.

* Vincent, in "Internal Secretion and the Ductless Glands," 1913, p. 116, states that he has never been able to find chromophil bodies in the spermophile.

The adrenals were removed from a series of animals in July, 1914. Five of them lived and hibernated during the winter of 1914–15. Twelve additional adrenalectomized animals were studied during the fall of 1915 and were found to hibernate under the same condition as the controls.

While these results show that the adrenals undergo fairly constant seasonal changes, they are just as much indicative of increased functional activity during the period of rut as of decreased activity during hibernation. It would appear that the adrenals do not bear any causal relation to hibernation for two reasons: First, the adrenalectomized animals, which certainly had only a minimum amount of adrenal tissue, hibernated normally. Second, the histologic changes noted in the hibernating animals were progressive, being found to some extent in the active animals in the autumn, and quite as marked in the animals which were sacrificed during the winter and which had not hibernated owing to the high temperature of the room.

The Pituitary.—The spermophile has a well-formed pituitary gland. It does not differ from the corresponding glands of other species except that the differential staining properties of the cells of the anterior glandular portion are not very marked. I have not been able to note any seasonal variation in the pituitary. In some of the pituitary glands of hibernating spermophiles I have found the same changes observed by Cushing and Goetsch in the woodchuck. These consist in an almost complete loss of the normally rather slight differential staining qualities of the granular content of the cells to acid and basic dyes, a decrease in the size of the cells, and an irregularity in the cellular grouping. However, these changes are not constant. In several hibernating spermophiles I have not been able to distinguish any changes in the pituitary glands. In many the changes are very slight. No mitotic figures were seen.

The inconstancy of the changes is proved very easily by a study of the glands having controls. I am not able to see any difference between the pituitaries of Gophers 225 and 227; 114 and 270; or 271 and 272.

The results of the study were as follows:

1. The sex glands undergo a definite seasonal variation but certainly do not play any part in the cause of the hibernating state or undergo any specific changes due to the torpid condition.

2. I have been unable to determine any changes in the thyroids

of the hibernating animal, and the fact that animals in which the thyroids were removed hibernated normally tends to show that these glands are not factors of significance in hibernation.

3. The very slight and inconstant changes noted in the parathyroids do not warrant any positive conclusion.

4. The thymus does not appear to undergo any uniform change.

5. The islands of Langerhans undergo changes so slight as not to justify a positive conclusion.

6. The adrenal glands undergo a fairly definite seasonal variation. The different changes are most marked during the winter and during the period of rut. However, the adrenals do not appear to be a specific factor in hibernation because the same changes were noted in animals sacrificed during the winter which had not been allowed to hibernate, and removal of the adrenals, which certainly reduced the adrenal substance to a minimum, did not in any way change the hibernating ability of the animal.

7. Some of the pituitary glands of the hibernating animals showed definite changes, but these changes were not constant.

CONCLUSION

It is impossible to state that some of the ductless glands are not of importance in relation to hibernation. New methods of investigation may demonstrate this relationship. However, the results of this study do not justify the assumption of any theory ascribing the phenomena to a lack of function of all or any one of the ductless glands.

BRIEF RECORDS OF MOST OF THE SPERMOPHILES WHOSE DUCTLESS GLANDS WERE STUDIED

No.   *A. Active Animals*

105 Female; weight 100 grams; captured April, 1915; pregnant; fasted for five days. Sacrificed May 5, 1915.

106 Male; weight 135 grams; captured April, 1915; fasted for five days. Sacrificed May 5, 1915.

108 Female; captured with two of her young in June, 1914. Very savage. Was kept in warm room during the winter of 1914–15, but hibernated when the temperature was allowed to decrease below 20° C. Sacrificed May 21, 1915.

147 Female; weight 125 grams; captured June, 1915. Sacrificed June 12, 1915.

148 Female; captured June, 1915. Sacrificed June 12, 1915.

149 Male; weight 143 grams; captured June, 1915. Sacrificed July 20, 1915.

174 Female; weight 144 grams; captured June, 1915. Sacrificed July 20, 1915.

175 Male; weight 134 grams; captured June, 1915. Sacrificed July 20, 1915.

192 Female; captured July, 1915. Had lactated. Sacrificed August 3, 1915.

198a Female; captured in the spring of 1915. Sacrificed August 14, 1915.

199a Female; captured in the spring of 1915. Sacrificed August 14, 1915.

204 Male; captured season 1915. Sacrificed September 14, 1915.

240 Female; very fat; weight 180 grams; captured early in the spring of 1915. Sacrificed September 24, 1915.

No.

241 Male; captured in the spring of 1915. Sacrificed September 24, 1915.

246 Female; captured in the spring of 1914. Both ovaries removed July 10, 1914. During the winter of 1914–15 was allowed to hibernate for short periods, but was active most of the time. Sacrificed September 21, 1915. Weight at time of death, 95 grams.

142 Female; weight 135 grams; captured May, 1915. Both ovaries removed June 3, 1915. Animal became slightly torpid at times during the autumn months, but was kept in a very warm room and did not hibernate. Sacrificed November 10, 1915.

146 Female; weight 126 grams; captured May, 1915. Uterus removed June 11, 1915. Sacrificed July 19, 1915. Weight at this time, 135 grams.

251 Female; weight 101 grams; captured July, 1914. Uterus and left ovary removed October 5, 1915. Sacrificed October 26, 1915.

225 Male; weight 110 grams; born in the spring of 1915. Animal placed in hibernating room without food at 12.00 M., November 11, 1915. Remained very active until November 20, when it seemed slightly torpid. Rectal temperature 20° C. Sacrificed at this time. (Control of Spermophile 227.)

114 Female; weight 120 grams; captured June, 1915. Animal was well supplied with food and kept in warm room. Did not become torpid while in captivity. Sacrificed February 2, 1916. (Control for Spermophile 270.)

268 Female; weight 55 grams; born in the spring of 1915. Animal had never hibernated. Food withdrawn but room kept warm, February 3, 1916. Sacrificed February 5, 1916. (Control for Spermophile 267.)

269 Female; weight 50 grams; born in the spring of 1915. Animal had never hibernated. Sacrificed February 24, 1916. (Control for Spermophile 220.)

271 Female; weight 140 grams; captured July, 1915. Had lactated that season. Did not hibernate while in captivity. Sacrificed February 28, 1916. (Control for Spermophile 272.)

275 Male; weight 105 grams; captured in the spring of 1915. Spleen removed July, 1915. Was not allowed to become torpid while in the laboratory. Sacrificed March 27, 1916. Genital tract showed the marked hypertrophy and hyperemia of beginning rut. (Control for Spermophile 274.)

278 Female; weight 85 grams; captured July, 1915. Had lactated in the spring of 1915. Did not hibernate during the winter of 1915–16. Sacrificed April 11, 1916. At necropsy the animal showed pregnancy of a few days' duration.

284 Female; weight 65 grams; captured July, 1915. Born in the spring of 1915. Did not hibernate during the winter of 1915–16. Sacrificed April 21, 1916.

No.	Time Hiber- nating	B. Hibernating Animals
267	12 hours	Female; weight 60 grams; born in the spring of 1915; kept under observation and it is certain that it had never become torpid until placed in the hibernating room without food February 4, 1916, at 4.00 P. M. It became torpid about 10.00 P. M. Was sacrificed February 5, at 10.00 A. M. Rectal temperature 11° C.
252	1 day	Fat female; captured in the spring of 1915. November 8, 1915, at 4.00 P. M., placed in room with temperature of 14° C. with no food. Had not hibernated previously during the season. Remained active until 10.00 A. M., November 9. Sacrificed November 10 at 10.00 A. M. Rectal temperature 14° C.
253	2 days	Fat female; captured in the spring of 1915. November 8, 1915, placed in room to hibernate, with no food. Did not become torpid for several hours. Sacrificed November 12, after hibernating for two days. Temperature of room at this time 9° C. Rectal temperature 11° C.
255	3 days	Fat female; captured in the spring of 1915. Placed in hibernating room, without food. Remained active for several hours. Sacrificed November 18, 1915, after hibernating three days. Rectal temperature 12° C.
127	4 days	Male; weight 150 grams; captured in the spring of 1915. Placed in hibernating room without food; remained there less than twenty-four hours. Sacrificed December 2, 1915, after being torpid four days. Rectal temperature 14° C. Room temperature 12° C.

No.	Time Hibernating	
227	5 days	Male; weight 108 grams; born in the spring of 1915. Animal placed in hibernating room, without food, at 12.00 m., November 11, 1915. Became torpid first November 16. Sacrificed November 20, at 10.30 a. m. Rectal temperature 10° C.
254	6 days	Very fat female; captured in the spring of 1915. When placed in hibernating room without food, became torpid very quickly. Sacrificed November 15, 1915, after hibernating six days. Rectal temperature 8.5° C. Room temperature for the six days varied from 5° to 10° C.
226	7 days	Male; weight 96 grams; born in the spring of 1915. September 9, 1915, both testes removed. Animal recovered from operation and increased in weight. Placed in hibernating room without food; sacrificed December 15, 1915, after hibernating seven days. Rectal temperature 9.5° C. Weight when sacrificed, 110 grams.
132	8 days	Female; weight 115 grams. Captured May, 1915. Placed in hibernating room without food; sacrificed December 11, 1915, after being torpid eight days. Rectal temperature 15° C.
259	9 days	Female; weight 100 grams; captured in the spring of 1915. Placed in hibernating room without food; sacrificed December 17, 1915, after hibernating nine days. Room temperature at this time 0° C. Rectal temperature 5° C.
256	10 days	Very fat female; captured in the spring of 1915. Placed in hibernating room without food; sacrificed November 20, 1915, after hibernating ten days. Rectal temperature 11.5° C.
260	15 days	Female; weight 85 grams; captured in the spring of 1915. Animal had been torpid continuously for fifteen days, although it had been torpid for a short time earlier in the season. Did not have access to food; sacrificed January 1, 1916. Rectal temperature 12° C.
170	20 days	Female; weight 145 grams; captured in the spring of 1915. Animal did not have access to food; sacrificed January 15, 1916, after being torpid approximately twenty days. Rectal temperature 14° C.
258	25 days	Male; weight 150 grams; captured in the spring of 1915. Did not have access to food; sacrificed December 11, 1915, after hibernating twenty-five days. Rectal temperature 12.5° C.
257	30 days	Very fat female; weight 195 grams; captured in the summer of 1915. Had lactated that season. Did not have access to food; sacrificed December 11, 1915, after being torpid thirty days. Rectal temperature 12.5° C.
117	35 days	Male; weight 165 grams; captured in the spring of 1915. Animal had access to food. Had been torpid thirty-five days. Sacrificed January 10, 1916. Rectal temperature 14° C.
261	40 days	Very fat female; weight 150 grams; captured in the spring of 1915. Had access to food. Sacrificed January 12, 1916, after hibernating forty days. Rectal temperature 2.5° C.
221	45 days	Female; weight 85 grams; born in the spring of 1915. Both thyroids removed September 20, 1915. Placed in hibernating room without food; sacrificed January 13, 1916, after being torpid continuously for forty-five days. Rectal temperature 6° C.
121	50 days	Male; weight 180 grams; captured May, 1915. Sacrificed January 13, 1916. It had been hibernating for fifty days without access to food. Had shown some signs of activity for a short time during this period but did not become active. Rectal temperature 5° C.
263	75 days	Female; weight 100 grams; captured in the spring of 1915. Sacrificed January 12, 1916, after hibernating seventy-five days without access to food. This animal was slightly active a few times during this period. Rectal temperature 12° C.
272	80 days	Female; weight 90 grams; captured in the spring of 1915. Sacrificed February 28, 1916. Had been hibernating without access to food for eighty days. Rectal temperature 19° C. Daily observations were not taken on this animal.

No.	Time Hiber-nating	
262	100 days	Male; weight 95 grams; captured in the spring of 1914. Hibernated at intervals during the winter of 1914–15. Food was withdrawn October 1, 1915, and the room allowed to approximate outside temperature. Animal immediately became torpid. Sacrificed January 12, 1916, after hibernating about one hundred days. Animal rather thin. Rectal temperature 11° C. Daily notes not taken.
266	125 days	Female; captured June, 1914. Hibernated when kept in cold during the winter of 1914–15. Placed in hibernating room and food withdrawn the latter part of September, 1915. Sacrificed January 27, 1916, after hibernating about one hundred and twenty-five days. Rectal temperature 17° C. Daily observations were not made.
270	150 days	Female; captured May, 1914. Hibernated at intervals during the winter of 1914–15. Was placed in hibernating cage, without food, October 1, 1915. Daily observations were not taken, but it is known that the animal was torpid most of the time, although at intervals it was slightly warm to the touch. Sacrificed February 28, 1916. Quite torpid; rectal temperature 21° C. Very thin. Weight 75 grams.
220	Indefinite	Male; weight 93 grams; born in the spring of 1915. Both thyroids removed September 20, 1915. Hibernated at intervals throughout the winter. Had access to food. Sacrificed February 24, 1916. Quite torpid. Rectal temperature 20° C. Very thin; weight 50 grams. No thyroid tissue found. Daily observations not taken.
228	Indefinite	Male; weight 82 grams; born in the spring of 1915; both testicles removed September 21, 1915. Hibernated at intervals throughout winter. Had access to food. Sacrificed February 28, 1916. Quite torpid. Rectal temperature 20° C. Weight 65 grams. Daily observations not taken.
135	Indefinite About 40 days	Female; weight 122 grams; captured May, 1915. Spleen removed May 28, 1915. Animal recovered from operation and became fat. December 13, 1915, placed in hibernating room with food. In the attempt to determine the reaction of the hibernating animal to excessive cold it froze to death January 13, 1916. Tissues of all organs were well preserved.
118	Indefinite About 45 days	Female; weight 105 grams; captured in the spring of 1915. Placed in hibernating room with food December 3, 1915. In studying effect of excessive cold upon hibernating animals it was frozen to death January 13, 1916. Tissues were in excellent preservation.
264	Indefinite About 40 days	Female; weight 95 grams; captured in the spring of 1915. Placed in hibernating room with food December 3, 1915. Was frozen to death during the study of the effect of excessive cold upon hibernation January 13, 1916. Tissues well preserved.
265	Indefinite About 40 days	Male; weight 95 grams; captured in the spring of 1915. Placed in hibernating room with food December 3, 1915. Was frozen to death during the attempt to determine the effect of excessive cold upon hibernation January 13, 1916. Tissue well preserved.

C. Active Immediately After Hibernation

237 Male; born in the spring of 1915; right adrenal removed September 23, 1915. Had access to food throughout winter. Hibernated at intervals. Sacrificed March 11, 1916. Animal very active at this time. Very poor weight—50 grams.

210 Female; captured in the spring of 1915; right adrenal removed September 15, 1915. Had access to food throughout the winter. Hibernated at rare intervals. Sacrificed March 11, 1916. Animal very fat; weight 110 grams.

126 Female; captured in the spring of 1915. December 12, 1915, placed in hibernating room without food. While daily observations were not made, it is known that the animal was very torpid although two or three times it was found to be active. At 9.00 A. M., March 11, 1916, animal was torpid; rectal temperature 15° C. Animal was placed in warm room and at 10.00 A. M. was very active. Sacrificed at 3.00 P. M. Weight 75 grams.

No.

273 Female; weight 95 grams. Captured late in the spring of 1915. Had lactated during the season. Hibernated at intervals during the winter of 1915–16. Had access to food. Was hibernating March 11, when it was placed in a warm room. Thereafter remained active. Sacrificed March 18.

231 Female; weight 200 grams. Captured in the spring of 1915. Ovaries removed September 22, 1915. Hibernated at intervals throughout winter 1915–16. Had access to food. Sacrificed March 18, 1915; weight at this time, 100 grams.

274 Male; weight 85 grams. Captured in the spring of 1915. Hibernated during the winter of 1915–16. Had access to food. Was torpid until March 11, when its rectal temperature was 20° C. When placed in a warm room, it remained active. Sacrificed March 27.

276 Female; weight 105 grams. Captured in the spring of 1915; hibernated during the winter of 1915–16. Had access to food. Active after March 11. Sacrificed March 27.

190 Female; weight 106 grams. Captured in the spring of 1915. July 23, 1915, complete removal of both thyroids. Animal hibernated during the winter of 1915–16. Had access to food. It was placed in a warm room March 11, and thereafter was never noted to be torpid. Sacrificed April 4; weight at this time, 83 grams.

273 Male; weight 145 grams. In excellent condition. The first animal caught in the spring of 1916. Captured and sacrificed April 11, 1916. Marked hyperemia and hypertrophy.

280 Female; weight 120 grams. Captured July, 1915. Had lactated during the season of 1915. Hibernated during the winter of 1915–16. Had access to food. Was not torpid after March 10. Sacrificed April 14, 1916.

281 Female; weight 145 grams. Captured and sacrificed April 14, 1916.

282 Male; weight 170 grams. Captured and sacrificed April 14, 1916.

283 Female; weight 110 grams. Captured and sacrificed April 17, 1916.

REFERENCES

1. Cushing, H., and Goetsch, E.: "Hibernation and the Pituitary Body," Jour. Exp Med., 1915, xxii, 25–47.
2. Polimanti, O.: Il letargo, Rome, Bardi, 1913, 683 p. (This is the most recent book dealing with the subject. It is thorough and gives a full bibliography.)
3. Gemelli, A.: "Su l'ipofisi delle marmotte durante il letargo e nella stagione estiva," Arch. p. le sci. med., 1906, xc, 941.

THE THYMUS IN ADULTS WITH ESPECIAL REFERENCE TO GOITER *

JOHN M. BLACKFORD AND WILFRED P. FRELIGH

During the past six years (January 1, 1910, to November 1, 1915) the Mayo Clinic has afforded opportunity for the study of data on necropsies of 1213 adults, 236 (20 per cent.) of whom at the time of their deaths were between the ages of puberty and thirty. The complete records in these necropsies and the gross findings in the thymus have stimulated very careful examination of the thymic fat body as a routine in 500 necropsies in the past two years. Careful microscopic study was made of all areas suggesting thymic tissue found by careful inspection of the cut surface of the thymic fat in multiple sections. The material thus obtained has seemed worthy of review for comparison with other recent work on this subject.

Deaths from "status lymphaticus" are always of interest, and the diagnosis and significance of a hypertrophied thymus in cases of goiter have been widely discussed, especially in recent literature.

Unexplained sudden deaths have often been attributed to status lymphaticus, and frequently this has been confirmed at autopsy by the finding of lymphoid or thymic hyperplasia. The first notable instance of a death attributed to status lymphaticus was that of Professor Langerhans' son, following the administration of diphtheria antitoxin. Our present knowledge of anaphylactic phenomena gives us a more probable explanation of this case. Various reports of deaths attributed to the thymus occur in literature, and perhaps the most remarkable of these is the celebrated Dawkes case. A woman who was being beaten by her drunken husband escaped and was pursued several blocks. She collapsed suddenly, and he kicked and pounded her until he discovered that she was dead. Necropsy revealed a hypertrophied thymus, and a diagnosis of "thymic death" saved the rascal from hanging. Most of

the deaths reported from this cause have occurred during anesthesia. Levy, who has examined records of some 60 sudden deaths from anesthesia, confirms our belief that such deaths are almost invariably associated with chloroform or ethyl-chlorid anesthesia. A series in the Mayo Clinic of 80,000 ether anesthesias without immediate death from anesthesia seems at least circumstantial evidence that the sudden deaths which occur when the patient is under an anesthetic are usually due to the anesthetic or the anesthetist and not to the thymus.

Chronic thymic intoxication as a cause of myocardial weakness, general debility, and poor resistance to toxemia has been widely discussed in recent years, particularly in relation to exophthalmic goiter. The facts regarding these hypotheses will be discussed later in this paper.

NECROPSIES ON ADULTS IN WHOM GOITERS WERE NOT PRESENT

In reviewing the records of 1096 necropsies of adults in whom goiters were not present we found marked hypertrophy of the thymus in 7 instances. In 3 it was found in persons who had died of sarcoma, this fact confirming the well-known association of hypertrophied thymus and sarcoma. The others were, in brief, as follows: (1) A woman thirty-six years of age, whose death was due to hemorrhage from placenta prævia; weight of the thymus, 22 gm.; (2) a boy eighteen years of age, dying in an epileptic attack; weight of the thymus, 7 gm.; (3) a man twenty-four years of age, whose death was due to a crushing injury to the head; weight of the thymus, 22 gm.; and (4) a woman thirty-nine years of age, whose death was due to obscure anemia; weight of the thymus, 18 gm.

Microscopic remnants have been found frequently but have not been significant. Our records indicate that hypertrophy of the thymus occurs rarely in adults, except those afflicted with goiter or sarcoma.

NECROPSIES ON ADULTS IN WHOM GOITERS WERE PRESENT

One hundred and fifty patients suffering from goiter have died and 117 necropsies have been recorded. Of these, 17 necropsy reports and 4 clinical histories in early cases were discarded because they were manifestly incomplete.

The series has been divided into hyperplastic and non-hyperplastic types, and each type has been subdivided by ages into three groups: Group I, patients under thirty-one years of age; Group II, patients from thirty-one to forty years of age; Group III, patients forty-one years of age or older. The exophthalmic goiters have shown a definite paren-

chymatous hypertrophy. No examination was made in cases that did not come to necropsy. To the "non-hyperplastic" goiter type belong all non-malignant cases not showing parenchymatous hypertrophy of the thyroid; cases classified by the clinician as non-hyperplastic toxic and non-hyperplastic atoxic cases.

EXOPHTHALMIC GOITER

Group I (Patients Under Thirty Years of Age).—Patients in this group show most constantly the definite course of the disease as described by Plummer. Plummer has shown that from the clinical onset the average duration of the disease to the first exacerbation is nine months, and that the greatest number of deaths occur at this point. Many of these patients become suddenly ill after a few months of vague disturbances, *i. e.*, acute prostration, nausea, vomiting, diarrhea, salivation, and extreme vasomotor phenomena. Weakness may be very marked. In most cases loss of weight is extreme, though in some there is no loss. Marked mental stimulation, often associated with euphoria, may approach the picture of alcoholic intoxication. In the worst cases the patient dies within a few days or weeks, presenting the picture of mental, physical, and cardiac exhaustion. Any surgical interference at such a crisis results in a high mortality.

In the thirteen patients under thirty years of age who died without being operated on the average duration of life was about eight months from the onset of the clinical symptoms. All these patients showed a questionable to moderate exophthalmos. The post-operative deaths in acute cases are, for the most part, similar to the "medical deaths." In the chronic cases the patients have usually lived through one or two such crises, but because of marked organic changes they were unable to survive the exacerbation of symptoms following surgical interference.

A marked degree of hypertrophy of the thymus was found in all but one of the 25 persons coming to necropsy. The one exception might well be omitted, since the patient was an extreme chronic cardiopath with a history of exophthalmic goiter five years before. There was no evidence of active intoxication at the time of death. The weights of the thymus in the 24 cases averaged 36 gm.: the smallest and greatest weights were 9 and 80 gm. respectively. From these findings we may assume that every young person with active exophthalmic goiter has marked hypertrophy of the thymus, regardless of the type of disease.

Group II (Patients Between Thirty and Forty Years of Age).—Three-fourths of the patients in this group had chronic disease of long duration, the average being eighty-four months. Six were acute cases (less than twelve months). These six patients were all more than thirty-seven years of age, a fact which suggests that they should be classified in the "menopause group," described in the discussion of Group III. The one

medical death was that of a woman thirty-nine years of age, an extreme cardiopath without active intoxication. She gave a history of disease of eleven years' duration. It should be noted that there are no medical deaths due to exophthalmic goiter of patients between the ages of thirty and forty years, although in patients coming to the Mayo Clinic the major incidence of the disease occurs in this decade. It would seem that the intense intoxications which are likely to prove fatal are exceptional in patients in the thirties. In general such cases are of long duration, and relatively marked cardiac insufficiency is the rule. In 10 of the 15 cases coming to necropsy the disease manifested itself in the previous decade.

In this group of 13 cases hypertrophy is constant, though not comparable in extent to that in the preceding group. The average fat-free weight of the thymus was 18 gm., with 3 gm. and 41 gm. as extremes, or one-half the average weight in the cases of Group I. An attempt was made to estimate by microscopic study the percentage of the thymus tissue present in proportion to total weight. We found that this group showed about 50 per cent., whereas Group I showed nearly 75 per cent.

Group III (Patients More Than Forty Years of Age).—The acute cases in this group are most striking; either the violence of the intoxication or a poor resistance, or both, causes these patients to be overwhelmed by the disease. They are prone to show pigmentation of the skin, which may even simulate Addison's disease, and their asthenic state is most distressing. Of all types of exophthalmic goiter, these are the most difficult to diagnose, and are doubtless often overlooked. The patients rarely show decided eye signs; only a slight Stellwag, such as might be due to hypertension or nephritis. This acute group might well be called the "menopause group." The mortality in this group of patients is higher than that of any others coming for treatment. Very severe organic changes, particularly cardiac, evidence the violence of the toxemia. The average duration of the disease is 7.4 months. Three patients died within three months from the onset.

In the chronic cases of this group the average duration of the disease is seventy months. Of the 22 patients, 11 were extreme cardiopaths, with fibrillation and great cardiac dilatation. In the other 11 there was definite to marked cardiac damage. Probably because these patients survive the acute onset of the disease and become hopeless cardiopaths the pigmentation seen may be that of the acute cases which have passed through the first crisis. Only 7 per cent. of the 44 patients dated the onset before the age of forty, whereas in Group II 50 per cent. dated the onset in the previous decade.

Hypertrophy of the thymus is found in patients in this group, though not to the same extent as in younger patients. In 19 of 36 necropsies no demonstrable thymic tissue was found. In the 17 remaining necropsies the average weight of the thymus was 13 gm.

Discussion

The hypertrophic thymus has been found in the 37 patients under forty years of age who have come to necropsy with active exophthalmic goiter. The thymus has been absent in 19 of 36 patients having an active exophthalmic goiter who died after the age of forty.

While a hypertrophic thymus has been found in 73 per cent. of 74 carefully studied cases of exophthalmic goiter, these figures do not give a true idea of its incidence. It is present in all patients under forty years of age and absent in half of those more than forty years of age.

The blood counts of these fatal cases were of interest on account of their negative value. Lymphocytosis was present and was more marked in the younger patients. The blood-picture of a leukopenia with a lymphocytosis has been described by Kocher as being of serious import. This was not borne out by our blood counts. As Plummer has observed, our average blood counts are identical in the fatal and non-fatal cases if the patients compared are of the same age.

Non-hyperplastic Goiter

In 32 post-operative deaths in cases of non-hyperplastic goiter there have been 26 necropsies. Medical cases will not be considered in this discussion because in the cases recorded the goiter was apparently of incidental importance.

Group I (Patients Under Thirty Years of Age).—There were three deaths; all those of young men of more or less delicate build, but apparently normal. One died the day of operation; one died three days after operation from mediastinal hemorrhage; and the third died suddenly following the administration of novocain for tonsillectomy two weeks after thyroidectomy under ether. The thymus weighed 100, 52, and 29 gm. respectively.

Group II (Patients Between Thirty and Forty Years of Age).—There were two necropsies in this group, neither showing the presence of a thymus.

Group III (Patients More Than Forty Years of Age).—Of 21 necropsies, there were 15 in which no thymus was found. Six in which there was a large thymus (averaging 33 gm.) were so striking that we attempted, though without success, to get some evidence of an associated clinical syndrome.

The patients in this group may be classified clinically as: 16 thyro-

toxic—3 with advanced cardiac disease; 3 with very large goiters; and 3 with large intrathoracic goiters; 6 surgical accidents, such as hemorrhage and infections, in good risks; and 1 case of esophageal diverticulum in which the removal of the goiter was incidental.

Chronic Thymic Intoxication in Goiter

Much has been written regarding a "thymic-toxic state," and particularly regarding a "thymic-toxic type" of exophthalmic goiter, in the belief that the rapid cardiac degeneration might be due to the thymus rather than to the thyroid intoxication.

Our records in general show that the most severe acute cardiac damage is seen in those violent intoxications in which the onset occurs after the age of forty; that is, in the "menopause group." These, as a rule, have a small thymus or no thymus. In every case of cardiac damage in which a thymus was found there was also definite parenchymatous hypertrophy in the thyroid, and in many of the worst cardiac conditions there was definite parenchymatous hypertrophy in the thyroid with no demonstrable thymus.

The findings submitted indicate that thymic hypertrophy and lymphoid hyperplasia should be considered as a result, rather than as a cause, of the intoxication in hyperplastic or non-hyperplastic goiter. Hypertrophy of the thymus probably depends on the presence of vestigial tissue at the onset of disease, which may regenerate under toxic stimulation. Therefore, hypertrophy of the thymus is universal in young people with thyroid intoxication, and often lacking in old people.

In every patient under forty years of age with exophthalmic goiter, and in every patient under thirty years of age with non-hyperplastic goiter, coming to necropsy, hypertrophy of the thymus has been found. The average weight of the thymus in the third decade was double that in the fourth decade and nearly three times that found in the fifth decade or later. In patients more than forty years of age one-half of those with exophthalmic goiter and three-fourths of those with non-hyperplastic goiter showed no evidence of thymus. In patients more than forty years of age with acute exophthalmic goiter the thymus, if present, was, as a rule, small, while in cases of long duration the thymus, when present, was usually large. In other words, hypertrophy of the thymus is inversely proportional to the age of the patient, and directly proportional to the duration of the disease.

THE ACTIVE CONSTITUENT OF THE THYROID: ITS ISOLATION, CHEMICAL NATURE, AND PHYSIOLOGIC ACTION *

EDWARD C. KENDALL

Two years ago I reported the isolation from the thyroid of a crystalline compound containing 60 per cent. of iodin.[1] At that time the complete details of the separation were not given. The reason for this was that when it was attempted to repeat the work and separate more of the substance, fourteen months of continuous effort and over a ton of thyroid were required to duplicate the results. The method employed at the time of the first isolation was hydrolysis of the alpha fraction of the split thyroid proteins with barium hydroxid and the separation of the resulting compounds according to the solubilities of their barium salts.[2] Eventually the stumbling-blocks which prevented the repetition of this work were found to be five in number:

First, heating the thyroid proteins or the alpha split products in the presence of metals other than nickel, and the heavy metals, silver, gold, and platinum. Heating an alkaline solution in the presence of iron, zinc, copper, lead, tin, or German silver results in destruction of the iodin compound. As the initial step was carried on by heating in a large iron vessel, several months' work was fruitless because of this reaction.

Second, acidifying an alkaline solution at a temperature above 40° or 50° C. It was shown eventually that this causes an alteration in the iodin compound, so that when it is next heated with alkali it is destroyed. At the time of acidifying there is no apparent change. The subtle action of acid was hidden behind this screen for many months.

Third, the failure to treat the iodin compound with carbon dioxid. The necessity of the presence of carbon dioxid for the separation of the crystals was discovered quite by accident, but it was later shown that unless the solution is treated with CO_2 it is impossible to separate the iodin compound in crystalline form.

Fourth, the effect of carbon dioxid in a warm solution. When a solution of the iodin compound is treated with carbon dioxid at a temperature above 70° or 80° C., iodin is broken off and the compound is destroyed. Similar treatment at a lower temperature has no such deleterious action.

Fifth, the condition of the desiccated thyroid itself. It was found that when some samples of desiccated thyroid were subjected to this process none of the iodin compound could be separated. The explanation apparently lies in the fact that the thyroid proteins were altered by bacterial action before they were desiccated.

During the first isolation of the crystals all these five interfering factors were unconsciously controlled, but it was only after many months of work that these reactions were understood and their importance appreciated.

The chemical properties of the iodin compound are a series of contradictions, changing according to the purity of the compound. This may be illustrated as follows:

When the compound is partially purified and contains from 10 to 40 per cent. of iodin, it is not dialyzable. The pure crystalline compound is dialyzable.

If the partially purified compound is boiled with hydrochloric acid, a tarry product results which apparently has but little physiologic activity. It seems highly probable that the iodothyrin separated by Baumann[3] twenty years ago by acid hydrolysis closely resembles the result of boiling the impure iodin compound with a mineral acid.

The partially purified compound is destroyed by carbon dioxid in a hot solution. The pure crystals may be boiled in the presence of carbon dioxid with no destruction.

The solubility of the barium salts is very confusing. At first nearly all the iodin compound is soluble in barium hydroxid. According to the treatment it may or may not become insoluble. Later it becomes soluble in barium hydroxid, but when finally purified in the crystalline form the iodin compound is practically insoluble in barium hydroxid.

The partially purified preparation is soluble in sodium carbonate and in alcohol. The purified crystals are insoluble in sodium carbonate and very insoluble in alcohol.

Even after the substance has been separated it does not cease to be annoying, as it may be destroyed by the action of sunlight.

Throughout the course of the separation there are many evidences

that the compound is tautomeric. A solution of the compound in sodium hydroxid when near the neutral point may spontaneously precipitate in heavy, flocculent form without being treated with acid or in any other way. This is apparently a tautomeric change within the compound.

If the pure crystalline substance is dissolved in alcohol containing sodium hydroxid, and acetic acid is added, the compound separates in fine microscopic needles which appear as rosettes. If, instead of acetic acid, hydrochloric or sulphuric acid is added, no separation of the crystals occurs. If, however, the alcohol is boiled off from a solution to which hydrochloric acid is added, the substance will crystallize after most of the alcohol has been removed. Analysis of the crystals obtained from alcohol by acetic acid, and when precipitated with sulphuric acid from water, shows an iodin content of 65 and 60 per cent. respectively. It would therefore appear that the substance crystallizes in combination with one molecule of sulphuric acid.

The free-base form containing 65 per cent. of iodin is also obtained by precipitating with carbon dioxid or boiling an ammoniacal solution. The two percentages of iodin in the free base and in the salt form with sulphuric acid would indicate a molecular weight of 586 (Figs. 235 and 236).

Although about 6 gm. of this substance has been isolated for several months, the percentage composition of the compound has not yet been determined because almost my entire time has been spent in a study of the physiologic activity of the thyroid.

Following the administration, on successive days, of the thyroid hormone there is always a latent period of from twenty-four to seventy-two hours after the first day before a well-defined physiologic response is evident. The exact length of time before the appearance of the symptoms varies in different animals and in man. This latent period holds true of the carbon dioxid output and the increase in the nitrogen elimination. Injection of the hormone causes no immediate drop in blood-pressure, and, perhaps most significant, there is no increase in pulse-rate. These observations show that the rapid pulse seen in cases of hyperthyroidism is not directly due to an increase in thyroid secretion alone. There must be other influences at work beside the increased production of the thyroid hormone. Since many observations have been recorded regarding the effect upon the blood-pressure of the extracts from normal and pathologic thyroids, it was of interest to find that the

purified thyroid hormone has no immediate effect when injected subcutaneously or intravenously.[4, 5] The same latent period which precedes the rise in pulse-rate appears to hold true in regard to the blood-pressure as well. Administration of thyroid under certain conditions

Fig. 235.—Crystals of the hydrochlorid of the alpha-iodin compound.

A

B

Fig. 236.—.1, Crystals of the hydrochlorid of the alpha-iodin compound. B, Alpha-iodin compound in the free-base form.

of high blood-pressure will bring the blood-pressure back to normal. It will not, however, greatly reduce the blood-pressure in a normal individual.

The typical symptoms following the administration of the thyroid hormone are increase in pulse-rate, nervous irritability with tremor, and increased appetite with later nausea and diarrhea. In order to produce these symptoms several successive daily doses are required before the animal or human being will respond. The single administration of twice as much of the substance as is required to kill an animal, when given in small daily doses, causes very little effect. It, therefore, seems probable that the continued presence of this substance in the body over a considerable length of time is required to call forth a physiologic response. This is another expression of the time factor in regard to thyroid activity.

A very interesting observation concerning the duration of the symptoms produced by the thyroid hormone is the fact that the normal person or animal may very rapidly recover from a severe degree of intoxication, whether or not the administration is continued. The spontaneous improvement of animals that are under the influence of the thyroid hormone after seven or eight days suggests that some form of tolerance is developed within the organism. An animal which has once been under the influence of the thyroid hormone reacts to a very much less extent when a second series of injections precisely similar to the first is given. This is another evidence of tolerance produced within the animal. Animals which have been injected continuously for as long as two months show well-marked intervals when the symptoms are more pronounced. Similar facts are observed in clinical manifestations of hyperthyroidism. The typical picture of exophthalmic goiter cannot be produced in the normal experimental animal by the administration of the thyroid hormone alone. It appears highly probable that the first vigorous response to the administration of the thyroid hormone closely resembles the condition present in exophthalmic goiter, but because of the ability of the animal to develop a tolerance these symptoms are very short lived. Even if the administration of the hormone is continued, the animal does not remain long in the same state of intoxication, as certain factors enter which have ameliorating effects. This development of a tolerance and the cessation of the typical symptoms of exophthalmic goiter in the normal experimental animal and in man suggest that in exophthalmic goiter the primary disturbance is not in the thy-

roid. In exophthalmic goiter the primary disturbance results in a stimulus of the thyroid which continues over long periods, and conditions are such that a sufficient degree of tolerance to the thyroid hormone is not developed. The fundamental difference between experimental hyperthyroidism as produced by the administration of thyroid and the condition in exophthalmic goiter is the ability of the organism in exophthalmic goiter to remain in a hyperthyroid condition. The normal experimental animal cannot continue to respond to the thyroid hormone in a similar manner.

The tremendous revolution occurring in cases of cretinism and myxedema following administration of the thyroid hormone and the picture following excessive administration of the substance to normal experimental animals or man clearly demonstrate that the action of the hormone is not confined to any one organ or any set of organs, but that it acts throughout every cell of the body. The hormone is apparently required for the life of the cells, and the presence of the thyroid and iodin throughout the realm of animal life suggests that it is a necessary constituent, not only of the higher forms of life, but also even down through unicellular forms. In the absence of the thyroid there is a loss of tone in the cells not only in the brain, the muscles, and the skin, but in the alimentary tract, so that nutrition, absorption, and assimilation are poor. On the other hand, excessive administration of the thyroid hormone appears to produce a hyperactivity of the cells. There is marked effect on the mentality, the absorption and assimilation of the food are greatly improved, and throughout the entire body, life, which had been dormant, is started anew.

When attempts were made to shorten the latent period following the injection of the thyroid hormone, some interesting results were obtained which at first appeared paradoxic. It is well known that administration of thyroid causes an increased nitrogen metabolism and also an increased carbon dioxid output. It, therefore, seemed probable that if amino-acids or sugars were injected into an animal in a continuous injection, the administration of thyroid should cause a greater effect than in an animal with normal metabolism. Administration of the thyroid hormone under these conditions, however, causes no apparent effect. Even though very large amounts of the thyroid are given, there may be no change in pulse-rate, no increase in nitrogen elimination or in carbon dioxid output. In other words, physiologic response to the thyroid hormone is dependent on more than the presence of the hormone.

Since the nitrogen metabolism is increased by administration of thyroid, it seemed probable that animals which had received a very rich protein diet for some time would probably react more vigorously than those that had received a carbohydrate diet. When this was tried, it was found that the former reacted not at all to the injection of the thyroid and that in order to produce the most vigorous response the starving organism was the most suitable. In order to throw some light on this question animals were injected with a continuous injection of phenolsulphonephthalein in conjunction with sugars and amino-acids, and it was found that in animals having a very high phthalein retention no response to thyroid was shown. Later it was demonstrated that the phthalein test under these conditions is really a test of the relation between the reducing power of the body and the supply of oxygen from the blood.[6] In animals responding to the administration of the thyroid hormone the phthalein output was always high; that is to say, the supply of oxygen from the blood was keeping pace with the demands of the tissues. This is one condition which must be present before thyroid activity results from the injection of the thyroid hormone.

There are probably many other factors, and if any one link in the chain is inadequate, there is no response to the injection of the hormone. The fact that the hormone produces the greatest effect in a starving organism when there is an increase in amino-acids in the blood,[7] and the fact that under proper conditions a very vigorous response is produced when amino-acids are being injected, suggest that in some way amino-acids and the thyroid hormone interact. But at this time no detailed evidence will be submitted. It seems certain that there is no other substance in the thyroid which is necessary for the production of hyperthyroid symptoms because these same symptoms follow the administration of the thyroid hormone to thyroidectomized animals, to cretins, and to persons suffering from myxedema.

The question of whether or not the thyroid contains another active constituent cannot be definitely answered. The physiologic activity of the beta group of constituents is not at all clear. It is impossible to produce toxic symptoms by administration of this portion of the thyroid, and it is impossible to relieve the symptoms of myxedema, but certain indefinite skin conditions seem to be relieved by this group of substances. It is not the result of the activity of the iodin compounds in beta constituents because it is possible to remove these and secure the same results. The non-toxic effect of the beta group of constituents

is in strong contrast to the alpha group, although they both contain iodin. The iodin-containing compound in alpha constituents has been isolated and its toxicity shown; the iodin in the beta compounds is in organic combination, but the nucleus to which it is attached is unknown,

Fig. 237.—Appearance of patient upon entering Clinic.

Fig. 238.—One year later. Patient in same dress.

and no relation of iodin to activity is evident. While no definite proof of the relation of the iodin compound in the beta constituents to the alpha-iodin compound is possible until the beta-iodin compound has been isolated in pure form, it seems highly probable that the iodin compounds in beta are intermediate stages in the elaboration of the alpha

compound from iodin taken with the food.   The chemical identity of the
alpha-iodin compound is established, and although a pure crystalline
substance, its structure is extremely complex, having a molecular weight
of 586.   It is theoretically impossible to pass by one operation from in-
organic iodids taken in with the food to the completely elaborated alpha-
iodin compound.   Intermediate products must exist, and doubtless
these are found in the beta group of constituents.   The amount of the
total iodin in the gland which may exist in the alpha form, that is, in-
soluble in acids, varies from 2 to 3 per cent. up to 40 or 50 per cent.   It

Fig. 239.—Appearance of patient upon entering Clinic.

Fig. 240.—After six months' treatment with the alpha-iodin compound. Patient had grown three and one-half inches.

is highly probable that some equilibrium exists between the two forms,
so that in normal conditions a constant percentage of the total iodin is
in the alpha form.   The rest is retained in the gland in the physiologic
inert beta form.   Under conditions of thyroid disturbance this relation
is disturbed, and in the acute stages of hyperthyroidism very little iodin
is found in the gland, and what there is is mostly in the beta form.   The
percentage of the total iodin which is in the beta form varies with the
duration and severity of symptoms.   By the analysis of a large number
of cases it is possible to follow this decrease in the total iodin as the acute
symptoms develop.   After the crisis has been passed it is readily shown

that the iodin in the gland increases and the percentage of the total iodin in the alpha form increases.[8] Since it is possible to produce hyperthyroid symptoms by the administration of the alpha-iodin compound alone, the small amount in the gland in the acute stages of hyperthyroidism is not to be interpreted as a cessation of the activity of the gland

Fig. 241.—Appearance of patient upon entering Clinic.

Fig. 242.—After six months' treatment with the alpha-iodin compound. Patient had grown three and one-half inches.

at this time, but is more correctly interpreted as a loss of storage capacity on the part of the gland. The production of the substance may be as great or greater than normal, but it is not retained in the gland.

EFFECT OF THE ALPHA-IODIN COMPOUND IN CASES OF CRETINISM AND MYXEDEMA

It has long been known that the growth of cretins is materially influenced by administration of desiccated thyroid. It was, therefore,

interesting to determine the effects of the alpha and beta compounds in this respect.

CASE 1.—A cretin, aged nine years, weight 16.8 kilos, height 93 cm., was given beta compounds alone for ten weeks. Observations on pulse-rate, weight, and height showed no appreciable change during this period. At the end of the ten weeks a small amount of alpha-iodin compound (0.5 mgm.) was included in the daily dose. As there was a rapid response, the pulse-rate increasing to 140, the dose was reduced to $\frac{1}{3}$ mgm. of alpha-iodin per day, and this amount was continued for six months. The patient's weight and height were taken on the following dates:

DATES	WEIGHT, KILOS	HEIGHT, CM.
January 4, 1915	16.30	92.5*
January 27, 1915	16.10	95.0
February 27, 1915	16.70	95.0
April 2, 1915	17.30	97.5
May 5, 1915	16.90	97.5
June 24, 1915	17.10	99.5
July 8, 1915	18.60	102.0*
August 5, 1915	18.86	105.4
September 4, 1915	18.86	106.0
October 16, 1915	19.43	106.0
November 13, 1915	20.45	106.7
January 16, 1916	20.68	109.2
February 15, 1916	20.00	109.9
March 17, 1916	20.68	111.1
April 16, 1916	19.54	111.1
May 16, 1916	20.91	111.8
June 18, 1916	21.36	112.1
July 14, 1916	21.13	113.0
August 16, 1916	21.59	114.9
September 17, 1916	22.04	115.6
December 5, 1916	22.95	116.2*

Although no apparent effect was produced with the beta constituents in respect to growth, administration of alpha-iodin was followed by rapid and continued increase. At the same time the mentality was markedly improved. Formerly the child was phlegmatic, not easily aroused, did not play with other children, and was backward in talking. She has greatly changed in appearance, manner, and desire to play and talk (Figs. 237 and 238).

In this case so little of the alpha-iodin compound was given that no toxic symptoms were produced and only a tonic effect resulted. Thyroid deficiency in cretinism can apparently be supplied by the administration of very small amounts (1/180 grain a day) of the alpha-iodin compound.

CASE 2.—A boy, ten years of age, who had not been treated with thyroid. His condition was typical of cretinism: dry, scaly skin, poorly nourished, distended abdomen, feeble mentality. After six months' treatment with the alpha-iodin compound there was very marked im-

* The observations on January 4, July 8, 1915, and December 5, 1916, were taken at the Mayo Clinic. The other measurements were made at the home of the patient.

provement; the skin was normal and distention of the abdomen had been relieved. There was also marked improvement in mentality. There was a rise in hemoglobin, and the general condition was excellent. The daily dose for the six months was ⅛ of 1 mgm. of alpha-iodin (Figs. 239, 240, 241, and 242).

CASE 3.—A young woman, twenty years of age. When she entered the Clinic her condition was one of extreme hypothyroidism: Dry, scaly skin, cold hands and feet even in summer, and great apathy and sluggish mentality. Hemoglobin, 20 per cent. This patient responded very rapidly to the alpha-iodin compound, and in less than three weeks

Fig. 243.—Appearance of patient upon entering Clinic.

Fig. 244.—After eighteen days' treatment, during which time the patient received a total of less than ½ grain of alpha-iodin compound.

showed very marked improvement. The condition of the skin was relieved, the hemoglobin rose rapidly and steadily to normal, and the sensation of cold was no longer felt in hands and feet. Mental activity was greatly increased, and all evidences of edema relieved. The entire amount required to produce this change was 18 mgm., less than ⅓ of 1 grain of alpha-iodin (Figs. 243, 244, 245, and 246).

CASE 4.—A woman, forty-seven years of age. During the previous ten years her activities had declined until she was almost in a state of helplessness. Her condition had been diagnosed dementia præcox elsewhere, and a hopeless prognosis had been given. She had received desiccated thyroid without effect elsewhere. She was extremely resist-

Fig. 245.—Appearance of patient upon entering Clinic.

Fig. 246.—After eighteen days' treatment, during which time patient received a total of less than $\frac{1}{3}$ grain of alpha-iodin compound.

Fig. 247.—Appearance of patient upon entering Clinic.

Fig. 248.—After twenty-four days' treatment, during which time the patient received the alpha-iodin compound.

Fig. 249.—Appearance of patient upon entering Clinic.

Fig. 250.—After twenty-four days' treatment, during which time the patient received the alpha-iodin compound.

Fig. 251.—Normal monkey before injection. Weight, 13½ pounds.

Fig. 252.—Same monkey after 72 daily injections of 1½ mgm. of alpha-iodin compound. Weight, 6 pounds.

ant to alpha-iodin, requiring enormous doses to bring about a primary change. In about three weeks reaction had taken place, the skin condition was changed to normal, the mental activity was greatly increased, the apathy was relieved, the edema was entirely reduced, and the patient left the Clinic so changed that her children no longer recognized her. After having reacted to the thyroid hormone her daily dose had to be reduced to 8 mgm. per seven days. If this amount is increased or decreased, unpleasant subjective symptoms follow (Figs. 247, 248, 249, and 250).

To show the toxic effect of the alpha-iodin compound, monkeys, goats, and dogs have been injected over long periods of time. The accompanying illustration is of a monkey, original weight 6½ kilos. After 72 daily injections of 1½ mgm. of the alpha-iodin compound it died (Figs. 251 and 252). Weight at death, 2.73 kilos. The toxic
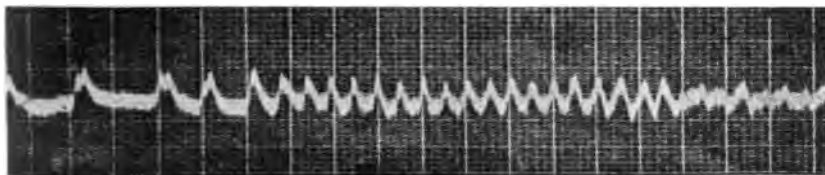
Fig. 253.—Ventricular fibrillation of a goat's heart produced by 11 successive daily injections of the alpha-iodin compound. Pulse-rate, 600.

effect upon the heart is shown in Fig. 253—fibrillation of a goat's heart produced by 11 daily successive injections of alpha-iodin compound.

REFERENCES

1. Kendall, E. C.: "The Isolation in Crystalline Form of the Compound Containing Iodin, Which Occurs in the Thyroid. Its Chemical Nature and Physiologic Activity," Tr. Assoc. Amer. Phys., 1915.
2. Kendall, E. C.: "A Method for the Decomposition of the Proteins of the Thyroid with a Description of Certain Constituents," Jour. Biol. Chem., 1915, xx, 501–509.
3. Baumann, E.: "Über das normale Vorkommen von Jod im Thierkörper," Hoppe-Seyler's Zeitschr. f. physiol. Chemie, 1895–96, xxi, 319–330.
4. Sanford, A. H., and Blackford, J. M.: "A Comparative Study of the Effects on Blood-pressure of the Extracts and Sera of Exophthalmic Goiter and of Other Substances," Jour. Amer. Med. Assoc., 1914, lxii, 117–122.
5. Levy, R. L.: "The Effect of Thyroid Secretion on the Pressor Action of Adrenin," Amer. Jour. Physiol., 1916, xli, 492–512.
6. Kendall, E. C.: "The Fate of Phenolsulphonephthalein When Injected into the Animal Organism. Factors Other than the Kidney Influencing its Retention," Jour. Amer. Med. Assoc., 1917, lxviii, 343–344.
7. Van Slyke, D. D., and Meyer, G. M.: "The Fate of Protein Digestion Products in the Body. V. The Effects of Feeding and Fasting on the Amino-acid Content of the Tissues," Jour. Biol. Chem., 1913–14, xvi, 231–233.
8. Wilson, L. B., and Kendall, E. C.: "The Relationship of the Pathological Histology and Iodin Compounds of the Human Thyroid," Amer. Jour. Med. Sci., 1916, cli, 79–91.

THE FUNCTION OF THE THYROID, NORMAL AND ABNORMAL *

HENRY S. PLUMMER

The thyroid performs its function so silently that but little regarding this function has been learned from the study of normal persons. Information has come from the manifestations associated with congenital. traumatic, or pathologic loss of the thyroid, or the evidence of excessive thyroidization associated with pathologic thyroids and thyroid feeding.

It is my purpose to present a mass of clinical and pathologic data so correlated as to support or refute many of the theories regarding goiter and thyroid function. I have found it necessary, in abstracting, to leave out statistical data, omitting to discuss the theories and presenting such alternate hypotheses as the facts suggest. I will, therefore, present here the entire abstract as hypothetic, leaving the segregation of facts and theories for the paper to be completed later.

The function of the thyroid is to furnish a hormone essential to cell metabolism. The clinical syndromes known as hyperthyroidism and hypothyroidism are the evidence of the departure of the individual from the normal attending deficient or excessive metabolism dependent upon this hormone. Sustained fluctuations in these reactions within limits that do not give rise to recognizable clinical syndromes may damage the individual. This may explain the goiter heart, in some cases unattended by definite evidences of hyperthyroidism. On this ground also may be built a theory that associates essential hypertension with and without goiter.

The normal thyroid never gives rise to definite clinical evidence of excessive or deficient function. The myxedematous patient can be so readily changed from the vegetating to an active intellectual organism that hypothyroidism, as a landmark in deficient thyroid function, can

be passed almost without comment. Definite clinical evidence of excessive thyroid function is seen only as it accompanies goiter. Goiter, as the term is commonly employed, is an enlargement of the thyroid, due, primarily, to an increase in the number of acini (adenomatosis); in the size of the acinar cells (hypertrophy); in the number of cells per acinus (hyperplasia) or the intra-acinar content. These changes are due to stimuli applied to the parenchyma cells and are, in the main, indicative of a functional activity above normal. The increased blood-supply demanded by a hyperfunctioning parenchyma may materially add to the size of the gland. Increase in the intra-acinar cells, secondary and degenerative changes that may lead to increase in the size of the gland, will not be considered further than to mention the probability that inflammatory and degenerative changes may at times stimulate the function of the thyroid as a whole.

On a correlation of clinical and pathologic data we may assume that there are two factors, or groups of factors, leading to goiter in man. As this grouping is primarily, though by no means wholly, based on the association of the clinical evidence of excessive function and hypertrophy, we may for convenience designate the first the major stimulus, the second, the minor stimulus. Wherein these stimuli or the factors accompanying them differ in degree, type, source, or association is open to question. That normal stimuli play an important part in the development of goiter can hardly be doubted. I will discuss in a future paper, but only mention here, the fact that colloid and adenomatous goiter are prone to develop when increased metabolism from normal physiologic causes makes a demand on the thyroid above the mean.

The parenchyma of post-natal thyroid is constituted of functioning, colloid-containing acini, plus, in an unknown percentage of persons, fetal acini. Application of the major stimulus to either fully developed or fetal tissue results in demonstrable hypertrophy, hyperplasia, and the hyperthyroidism characteristic of exophthalmic goiter. In this condition the highest degree of hypertrophy probably represents the height of thyroid productivity. Hyperplasia results when the stimulus is forcing the cell above its capacity which may be limited by beginning exhaustion from overwork, lack of material for its product, etc. Hypertrophy and hyperplasia may be co-existent in the thyroid or an acinus, though it is not probable that the cell can hypersecrete when undergoing division.

The minor stimulus applied to prenatally developed colloid-containing acini results in a hypertrophy of lesser degree and hypersecretion,

'16—34

or hypersecretion without at least a readily demonstrable increase in the size of the cell. Colloid is deposited in excess. This constitutes the colloid goiter. Rarely hypertrophy is marked and it is possible that hyperplasia may supervene. This hypertrophy and hyperplasia may be present without accompanying clinical evidence of hyperthyroidism, and does not give rise to the syndrome of exophthalmic goiter.

The application of the minor stimulus to the fetal acini results: (1) In the formation of new acini (?); (2) functioning of the acini; and (3) hyperfunctioning of the acini, with or without the deposit of colloid above the normal, with or without demonstrable hypertrophy. Whatever the inception of the adenomatous process, the acini once active seem, in the main, to functionate and follow the same pathogenetic laws as the acini of colloid goiter. In a small area of glands may be seen all types of acini—from the fetal without a lumen to the hypertrophic and hyperplastic. It is the inclusion of fetal acini and the arrangement of sustentacular tissue to be expected from the development of new gland-mass from belated fetal rests, rather than the character of the functioning acini that distinguishes adenomatous thyroid. This lower grade adenomatous tissue is more sensitive to stimulation, as is evidenced by its greater tendency to hyperfunctionate and degenerate.

That the same stimulus applied to fully developed thyroid and fetal thyroid will result respectively in colloid goiter and adenomatous goiter, correlates with clinical observation. This is based largely on the incidence of simple colloid and adenomatous goiter throughout the decades of life and the incidence of hyperfunction in the two types (data will be included in the published paper).

The known products of the thyroid are: colloid and its hormone, the alpha-iodin compound of Kendall. The thyroid secretes into its acini (externally) colloid, iodin, and perhaps its hormone. It secretes into its circulatory channels (internally) colloid and alpha-iodin. The time relation of these two phases cannot be definitely pointed out but it seems probable that while one or the other is prone to predominate, they may be coincident. Whether the phases be coincident or alternate, the sum total of alpha-iodin delivered into the circulation during a prolonged period in which colloid is being deposited is in excess. The deposition of colloid in excess is in the main indicative of a hyperfunctioning gland. This does not imply that the degree of activity can be determined by the amount of colloid present at the time of its removal. It may somewhat further eludicate the conception to apply the term "cystic" to

acini which as an immediate result of the degenerative changes are functionless or relatively functionless retention pockets.

The normal thyroid studied histologically is a relatively dormant-appearing gland. Under mean conditions the amount of its hormone required is small; it is probable that it does not have to fluctuate rapidly to meet unusual demands, and that there is relatively little change in its intra-acinar content. The greater part of the alpha-iodin may be supplied by simply remodeling the molecule returned from the tissue but little changed in its metabolic function. The goitrous thyroid may have long periods when its function is not above the normal. We cannot recognize histologically the hyperfunctioning gland except as hypertrophy is present.

It is self-evident that stimulation of the thyroid will not result in excessive production of its hormone if iodin is not available. Lack of available iodin and strong coincident stimulation may be one of the factors in producing hyperplasia. The work of Marine, Bensley, and others suggests that this is true of the hyperplasia of dogs, opossum, etc. It is not probable that the administration of iodin ever reduces the output of the thyroid hormone. It will increase it if the previous supply is not in excess and the thyroid is under high stimulation. In the paper I will present evidence to support the concept that the administration of the thyroid hormone will put the gland at relative rest, provided the demand is not above the capacity of the gland. These concepts afford a reasonable basis for correlating the many discordant results following the administration of iodin and thyroid to goitrous man and animals.

The majority of cases of colloid goiter have their inception between the fifteenth and eighteenth years; are prone to give clinical evidence of excessive function from the seventeenth to twenty-first years; again enlarge with the high metabolism of pregnancy and with or without the clinical evidence of hyperthyroidism, give rise to a damaged heart between the thirty-fifth and fortieth years. After the fortieth year, 27 per cent. of the cases coming to the consultant have blood-pressure readings attributable to arterial hypertension. During the periods of increased functional activity the parenchyma may show demonstrable histologic evidence of cell hypertrophy. High degrees of hypertrophy are unusual.

Adenomatous goiter follows much the same course. It is less apt to be accompanied by hyperthyroidism previous to the thirtieth year; after the thirtieth year it gives rise to much higher degrees of hyperthyroidism

than does colloid goiter, and this without hypertrophy of the parenchymal cells. The incidence of exophthalmic goiter gradually rises to the thirtieth year and then falls to the sixtieth year. Colloid and adenomatous goiter predispose but slightly, if at all, to exophthalmic goiter, though the stimulus that gives rise to the hypertrophy of the latter will also stimulate the development of adenomas.

That the thyroid plays an important part in metabolism and that the evidence of high metabolism dominates the clinical syndrome of hyperthyroidism is generally recognized, but to what extent the conceptions of others approach that of the author is indeterminable from literature; namely, that the rate of metabolism is dependent upon the thyroid hormone, that this function is not specific for certain tissues, but is common to all the cells of the organism. Increase or decrease in the rate of the metabolism dependent on this hormone to a sufficient degree gives rise to the clinical syndromes of hypothyroidism and hyperthyroidism. The normal thyroid undoubtedly responds to relative exhaustion of its hormone by the metabolic activity stimulated largely by nervous impulses. The correlation of the physiologic reactions characterizing the syndromes clinically recognized as hyperthyroidism and that of these reactions, with the histopathology of goiter, must to a certain extent remain hypothetical until we are able to determine the conditions under which they are attributable to a primary excess of the thyroid hormone or a primary high rate of metabolism demanding this hormone.

However, without this knowledge, an analysis of these syndromes alone leaves little, if any, ground for doubting that the rate of metabolism in the tissues is dependent on this hormone. In the paper I have attempted to discuss in detail the data in support of this theory. I will only mention here that we have learned to recognize and determine the degree of hyperthyroidism on the local evidence of a hyperfunctioning thyroid and the physiologic reactions attributable to stimulation, depression, or degeneration of the more highly differentiated fundamental tissues of the organism.

Prominently, but less easily analyzed, are the reactions in the secretory tissues. Here the direct action of the hormone is overshadowed by the functional activity supporting the metabolism of the more fundamental tissues. A conception of the physiologic pathology of exophthalmic goiter can be visualized in a general way by multiplying all of the normal physiologic reactions, taking into consideration the exhaustion and degenerative changes that would of necessity result.

PREOPERATIVE CONSIDERATIONS OF EXOPH-
THALMIC GOITER *

DAVID M. BERKMAN

— - ———

For purposes of correlation I shall briefly state the following accepted theories:

1. Exophthalmic goiter is a pathologic condition of the thyroid in which, by hypertrophy or actual hyperplasia of the secreting tissue, relatively tremendous amounts of the normal thyroid secretion are thrown into the circulation.

2. To the best of our present knowledge, thyroid secretion in its normal or physiologic dosage is the stimulant control over organic function as a whole. It is, therefore, essential to the proper maintenance of physiologic activity.

3. The condition brought about by oversecretion is a condition of excessive stimulation of practically the entire composite physical and mental mechanism. The result of a continuation of this excessive stimulation is organic degeneration which is most apparent in the cardiac and nervous system.

It is not my purpose to contrast for effect the medical and surgical therapeutic measures. Let me merely state that the analysis of not only our experience, but also the experience of competent observers at large, convinces us that in the majority of cases surgery, while by no means ideal, offers the greater chance of permanent relief. In thyroid work the question presenting itself to the surgeon is the mortality rate, and we are firmly convinced that the delicacy of thyroid surgery lies not alone in operative technic but equally in the accurate estimation of the patient's condition and power to withstand stress. The operative mortality at the Mayo Clinic for the successive years from 1910 to 1915, inclusive, was 4.8, 3.18, 2.6, 3, 2.89, and 2.63 per cent. Following the appreciable drop after 1910, the variation is not great. The material for

this paper is drawn from the hospital mortality records of patients operated on for exophthalmic goiter during 1914 and 1915. These were all definite and unmistakable cases of hyperthyroidism manifesting the cardinal signs and symptoms. The thyroids were proved histologically to be hyperplastic or hypertrophic in all but one case, which was questionable. This patient, however, gave an unmistakable history and there was definite exophthalmos. I shall designate the degree of condition by a numeric figure on a basis of one to four (Table 1).

TABLE 1.—EXOPHTHALMIC GOITER
(Hospital mortality, 1914 and 1915)

Number of deaths.....................................24
Average age of patients...............................34.8 years
Age of youngest.......................................14   "
Age of oldest...55   "
Average length of positive history.................... 5   "
Longest definite history.............................16   "
Shortest definite history (2 patients)................ 6   weeks
Average degree of present intoxication................ 2.6
Degree of severity (13 cases)......................... 2
Degree of severity (9 cases).......................... 3
Degree of severity (2 cases).......................... 4
Evidence of cardiac deterioration (6 cases)........... 0
Evidence of cardiac deterioration (7 cases)........... 1
Evidence of cardiac deterioration (7 cases)........... 2
Evidence of cardiac deterioration (3 cases)........... 3
Evidence of cardiac deterioration (1 case)............ 4

An analysis of Table 1 demonstrates several striking facts: (1) The length of definite history has very little bearing on the operative risk. (2) Cardiac deterioration as evidenced by cardiac enlargement, irregularity of the action of the heart and signs of incompetence are remarkably in the background, although present to some degree in all but six cases. I say "in the background" because of the relatively large number of patients suffering from an equal degree of heart involvement who were successfully operated on. The degree of present severity is more or less pronounced in all, and probably underestimated in many instances by the recorder. Herein would seem to lie the most tangible factor. Five patients gave histories of having had a more or less typical crisis within a month previous to coming for examination. Two of these crises were two weeks prior. Twelve, 50 per cent., gave no definite history of crisis, and in the cases of the remaining seven the crises had occurred far enough in the past to make them negligible.

It is an undoubted fact that recent crises add to the risk of surgery, although in comparatively few of the cases reported does this history manifest itself. Table 2 indicates the types of operation performed.

differentiating the preliminary work safely performed in each instance. One patient died immediately after an injection of hot water. In explanation I might say that this was a case of extreme intoxication from which it seemed impossible for the patient to recover. The injection was attempted in the hope of turning the tide in her favor before the power of recuperation was entirely lost.

TABLE 2.—OPERATIONS

Thyroidectomy (recurrence after previous thyroidectomies)	3
Thyroidectomy (preliminary—2 ligations, 2 hot-water injections)	1
Thyroidectomy (preliminary–single ligation)	3
Thyroidectomy (preliminary—double ligation)	1
Single ligation (preliminary—single ligation)	3
Thyroidectomy (preliminary—2 single ligations)	5
Ligation	3
Hot-water injections	1
Thyroidectomy	4
	24

With the possible exception of the four primary thyroidectomies these cases were all recognized as definitely poor surgical risks. The patients were not operated on out of hand, but were kept for varying lengths of time under close observation, for the most part in hospital medical wards. Surgeon and internist working together endeavored to select the proper time and course of procedure, and everything possible was done to lower the susceptibility to operative interference. I wish to draw special attention to the value of Porter's hot-water injection. While not absolutely devoid of risk, as evidenced by one death recorded in this report, the risk is practically negligible. I do not wish to enter into a discussion of the actual benefit this procedure may bring to the patient, as this is a question open to much criticism. However, I have seen many cases in which the injection was followed by immediate and definite improvement in the patient's condition. Its real value lies in the fact that it is a fairly accurate indication of the ability of the patient to undergo surgical interference with the thyroid. In many instances successful ligations had been done once and even twice before the operation from which the patient did not recover. (Eight patients, one single ligation; five patients, two single ligations; and one patient, a double ligation.) The patients in this series of cases received, let us say, medical treatment. The term is misleading. It implies that he receives an active and more or less standardized course of treatment from which, and definitely attributable to which, appreciable beneficial results may be expected in the majority of cases. Balfour sums up medical treatment as follows: "Rest,

which is above all the most important, and the treatment of special symptoms." According to Balfour, no one measure has given sufficiently consistent results to be retained as a permanent remedy. Bromids, phosphorus-preparations, serum of thyroidectomized animals, Beebe's cytolytic serum, x-ray exposures with the Coolidge tube, belladonna and quinin, thyroidectin, etc., have been used extensively enough and over a sufficient period to establish their merits. Of these, the x-ray probably produces the most decided results both theoretically and actually. Of 23 patients, Fisher reports 6 cured and 5 improved. Pfahler and Mc-Donald went extensively into the literature of x-ray treatment which covered many case records. They state that in the main results were good but temporary. However, they felt it was hardly possible to draw definite conclusions from statistics. The results from the use of the x-ray are delayed and require many repetitions of the treatment. Our experience has been that practically no dependable beneficial results are obtained in less than a month's time. Moreover, in the cases comprising the greater surgical risks, the excitement and mobilization incident to x-ray treatment usually offset whatever early benefits patients may receive. The effect of attempts at symptomatic relief by drugs is more apparent on the anxious friends and relatives than on the patient himself. The common occurrence of gastric irritation causes a quite natural hesitancy on the part of the physician to administer medicine orally. Digitalis is fairly well borne and of considerable value in the group of cases in which prostration is due to secondary cardiac deficiency. It is, however, useless or even worse than useless in those cases in which active thyroid intoxication is the debilitating factor. Boyd limits the treatment to a simple bland diet, mainly of milk, and complete mental and physical rest.

Our patients have been placed in bed and their clothing taken from them—they are relieved, so far as possible, from mental and physical strains. The question of operation is left indefinitely in the future, although far from dreading it, almost invariably the patient attempts to hasten its performance to an extent frequently embarrassing to the physician, who must daily impress him and his family with the great importance of the pre-operative period. Occasionally very little improvement is gained and a few patients are sent home to continue the rest treatment under the care of their local physician. These patients usually return after a period of several months in a condition of repose and increased strength which permits the performance of ligation with com-

parative safety. The weeding out of these patients must assuredly lower the mortality. The early cases are by no means the preferred surgical risks as a group. To quote from Mayo: "Some cases run an acute course to death in the first months; a slightly larger number, in the latter half of the first year, at which time the most marked effect is shown in the heart, liver, kidneys, and nervous system. It is during this period that the operative mortality is the highest."

Practically all of the questionable operative risks in this series of cases were passed on by Plummer, to whose judgment and experience the low operative mortality may be attributed in part. It is interesting to note that the death rates of the years 1912 and 1915 are practically identical. This would seem to indicate that there is a low-water mark, below which in handling a large number of cases annually it would be nearly impossible to go without unjustly refusing operation to a number of patients admittedly surgical risks, but who have a right to the chance of surgical relief after having been informed of the exact conditions and possible results.

SOME PHASES OF THE DIFFERENTIAL DIAGNOSIS OF EXOPHTHALMIC GOITER *

WILLIAM A. PLUMMER

This paper is confined to a discussion of the differentiation of exophthalmic goiter from neurasthenia, the most frequent condition with which it is confused. Whether we designate the latter nervous irritability or exhaustion, x-disease or neurasthenia, we all recognize this large group with its protean symptomatology and its lack of pathology and fatality, in which a perverted mental attitude is at least a predisposing factor.

The symptomatology of neurasthenia is so varied and is so apt to conform to that of the disease which the patient most fears, that at times the differential diagnosis is difficult or impossible. The absence of a definite clinical picture characteristic of the condition would lead to error more frequently were it not that in exophthalmic goiter we have a disease with a very definite symptomatology, and a complex which does not measure up to this should be looked upon with suspicion. We will be greatly aided in the differential diagnosis if we keep in mind that hyperthyroidism shows in its signs and symptoms as definite a reaction, dependent upon the dosage, as does alcoholism. It is as unwarranted a mistake to assume that headache associated with a small colloid goiter in the absence of increased pulse-rate or other signs means hyperthyroidism, as it is to assume that vomiting in the absence of an alcoholic breath or mental disturbance means acute alcoholism. Again, if we discover a pulse-rate of 120 associated with cold dry hands, we can at once nearly exclude hyperthyroidism, because a dosage sufficient to produce such a tachycardia will of necessity cause a vasodilatation with a warm, moist skin.

We will first consider the differential evidence which may be gleaned from the patient's history of the course and symptoms. Marked fluctuations in the severity of the symptoms, even though they may not have

been evident previous to the first examination, are typical of hyper-thyroidism. Neurasthenia also shows remissions, but exophthalmic goiter runs a wave-like course which gives a picture that is different. Though there may be shorter waves superimposed, the wave length as a whole is measured in weeks or months, not in hours or days. Even when repeated, symptoms which are severe one day, but are followed in a few hours or days by a reversion to an apparently normal condition, cannot be considered the result of exophthalmic goiter. The wave is frequently topped by a crisis during which all the nervous symptoms become aggra-vated and there is an added loss of appetite, diarrhea, and painless vomiting.

Because of the influence of text-book descriptions, the mistake of placing too much importance on a history of nervousness, palpitation, and tachycardia is frequently made. It is true that nervousness of a certain type is characteristic of exophthalmic goiter, but it is a sign rather than a symptom. Its manifestations are noticed by friends of the patient either before she herself has become conscious of their existence or at a time when she tries to hide or belittle them. Early in the disease the patient will ascribe this restlessness to a natural tendency to be active. It may be first evidenced in an increased desire to make money or an unusual neatness in the care of the house. The patient's assertion that she is nervous is in itself no indication of hyperthyroidism, and tachy-cardia with palpitation is found in too many other conditions to lead to a diagnosis of exophthalmic goiter in the absence of signs and symptoms on which less stress has been laid, but which are more distinctive. Hyperthyroidism results in an increased metabolism which nature at-tempts to care for by demanding more food, water, and air. As long as this exaggerated process takes place entirely at the expense of an abnor-mal intake, there will be a gain in weight and often an unusual sense of well-being, but when increased fuel cannot keep pace with increased demand, and metabolism must take place at the expense of body tissues, there will be a loss of weight and strength. Thus, an increased appetite, though it may be lost for short periods, is one of the earliest and most constant symptoms of exophthalmic goiter, and as it is seldom associated with the conditions which must be differentiated, it is certainly the most reliable single symptomatic guide. As these patients are unusually free from introspection, and as the nature of the symptom is such that it often goes unnoticed, repeated questioning is sometimes necessary to disclose an increased food consumption. Without dieting or other ob-

SURGERY OF THE THYROID *

EDWARD STARR JUDD

Very little is known regarding the etiology of the different types of enlargement which occur in the thyroid. Some observers believe that certain types of enlargement are the middlemen, so to speak, and that the real lesion and basis of the trouble are in the cardiovascular or nervous system. Although this may be true, there is a definite syndrome accompanying the different kinds of goiter. Furthermore, these symptoms will subside after the condition of the thyroid has been remedied.

The surgical treatment of cysts, adenomas, and colloid enlargements of the thyroid has been practised for a great many years, especially in Switzerland where such conditions are so common. Only comparatively recently have operations been performed for the relief of toxic symptoms produced by thyroid changes. Basedow, in 1840, first thoroughly described cases of exophthalmic goiter. By far the most important work in the development of the surgery of exophthalmic and thyrotoxic goiters has been done in this country by Crile, C. H. Mayo, and Ochsner. Even now operative results are not perfect, yet the progress made in the surgery of the thyroid in this country in the past twenty years is certainly one of the most, if not the most, important advancement made in surgery during that time. It is now generally conceded that most forms of goiter require surgical treatment for permanent relief. However, there is one form, the so-called adolescent goiter, that responds to medical management; and often some of the milder toxic types may be relieved without operative interference.

It is not my purpose to attempt to cover in this paper all the phases of treatment for lesions in the thyroid, but to present more especially a classification of these cases. Enlargements of the thyroid fall into four distinct groups, based on the clinical features and the histologic changes in the gland: Group I, simple colloid goiters, either of the adolescent

type or those produced by small adenomas which often develop about
the time of the menopause. Group II, adenomatous pressure thyroids,
characterized by a single large adenoma often accompanied by a number
of smaller ones. Group III, toxic goiters, including those designated as
hyperplastic and also the so-called degenerating adenomas or thyro-
toxicosis (Plummer). Group IV, malignant goiters.

Group I.—Simple goiters most often occur in young girls at puberty
and are frequently spoken of as physiologic enlargements. They are
not always accompanied by symptoms; and when symptoms are present,
it is frequently difficult to determine whether they have resulted from
this type of thyroid. The increase in the size of the thyroid is due
chiefly to the growth of colloid, although often there are areas of quite
definite hypertrophy. Usually the gland is soft and lobular and is gen-
erally enlarged. In some instances in which the enlargement of the thy-
roid is the only noticeable evidence of trouble the diagnosis is easy, but
when the patient is nervous and hysteric, as girls of this age may be,
the differential diagnosis may be difficult. The difficulty lies in distin-
guishing between the nervous features noticeable in a purely nervous
person with enlargement of the thyroid and those observed in a person
suffering from a mild degree of hyperthyroidism. In both instances the
thyroid enlargement may be of practically the same degree and consis-
tency. It is probable that at puberty many girls have a very slight degree
of hyperthyroidism, which may persist for some time and then subside.
The exophthalmic goiter patient is seldom hysteric. The tremor asso-
ciated with true hyperthyroidism is finer and more regular. A true
bilateral exophthalmos is characteristic of hyperthyroidism. Muscular
strength is more impaired in the true goiter patient. The pathologist,
even after histologic sections, cannot always say whether there is a true
hypertrophy. For this reason it would seem that there cannot be a great
deal of difference between the two types. The course of the adolescent
goiter varies. A large percentage subside within a few years and the
enlargement disappears. Often small doses of iodin will diminish the
glandular enlargement and relieve the symptoms. In other patients the
gland continues to increase in size, causes difficulty in breathing and
swallowing, and may produce choking. If the gland continues to increase
in size the enlargement may be at least partly due to the development of
adenomas within the colloid growth. Often growth is so slow that pres-
sure symptoms are not produced for many years, but usually if an
adolescent goiter does not disappear within a very few years, it will
continue to develop. In some instances the growth becomes very large
and produces marked pressure symptoms, as well as evidences of in-
toxication. The treatment in this group of cases varies. A simple
adolescent goiter should be given an opportunity to subside under proper
management, and if it does not disappear after puberty is well estab-

'16—35

lished, it should be removed. Operative treatment is advisable especially if the enlargement begins to increase, as it will surely make pressure and may possibly change its form and become toxic. Colloid enlargement may persist until about the menopause without producing marked symptoms, and then cause a very severe intoxication. For this reason it is advisable to remove the enlargement before the extreme degree of intoxication has occurred.

Group II.—The characteristic symptom in the cases in this group is pressure. The enlargement is due to the presence of the adenomas. The remaining part of the thyroid is apparently normal. The enlargement may be present for some time before symptoms arise. The first symptoms are usually choking, a sense of pressure, and shortness of breath on exertion. The tumor may increase greatly, producing marked deformity of the trachea and larynx, and perhaps a paralysis of the recurrent laryngeal nerve. These tumors are round, hard, definitely encapsulated, and move freely in the neck during the act of swallowing. They are definite adenomas and are sometimes cystic.

Surgical interference offers the only means of relief for this type of enlargement. The adenoma must be removed, and if necessary, a part of the thyroid tissue surrounding it. These patients frequently say that they are not inconvenienced by the enlargement at all, and they are rather inclined to put off surgical treatment. I believe it is much better to remove the adenoma before any nervous or toxic symptoms develop, as more of the danger in these operations results from the condition of the patient at the time than from the operation itself.

Group III.—The goiters of this group may be divided into two distinct types. One is comprised of the hyperplastic thyroids producing the symptoms of exophthalmic goiter, the other is characterized by the toxic degenerating adenomatous thyroid producing what Kocher calls the "goiter heart." Although these two types differ in many respects, it is entirely possible that the symptoms are produced by the same agent or toxin. An exophthalmic goiter is a definitely hyperplastic thyroid. Hyperplasia is usually present throughout the entire gland. Although a small part of the thyroid may appear to be nearly normal, areas of hyperplasia exist in other portions of it. Usually there is a general enlargement of the gland, although sometimes the most severe symptoms are noted when the gland is barely palpable. Occasionally the gland is not only hyperplastic, but contains adenomas. Sometimes after the polar vessels have been ligated several months adenomas will be found in the hyperplastic gland. This type of thyroid is usually firm, hard, and very vascular; on section it appears cellular and without a great deal of colloid. Glands of the thyrotoxic type vary considerably. A patient who has only a small adenoma of the thyroid may have a very marked toxemia. Other thyrotoxic patients may have general diffuse colloid enlargement of the thyroid with small adenomas distributed throughout

the gland. The enlargement is of the colloid adenomatous type; in some instances the colloid predominates, in others, the adenomas. The degree of intoxication seems to coincide with the amount of degeneration in the adenomas and the surrounding thyroid tissue. Exophthalmos is characteristic of the exophthalmic goiter, and is never seen accompanying the purely thyrotoxic gland. A patient suffering from exophthalmic goiter has typical tremor, tachycardia, nervousness, usually marked loss in weight, and characteristic metabolic changes may be observed. The thyrotoxic patient has no definite tremor, though there is often nervousness from exhaustion. The pulse is that of a dilated and damaged heart, and usually there is a marked increase in blood-pressure. In most instances a person suffering from a thyrotoxic goiter has more actual damage to the heart muscle. Möbius was the first to suggest that there may be an oversecretion in the gland in exophthalmic goiter. There is a theory that in thyrotoxic goiter the symptoms are produced by the absorption of the products of degeneration in the adenomas or in the thyroid itself. The administration of iodin and different preparations from the thyroid frequently seems to relieve patients suffering from hyperplastic goiters. On the other hand, iodin, especially, seems to increase the symptoms in the thyrotoxic patient. Ligation of the thyroid vessels and injections of boiling water into the gland often greatly relieve the symptoms accompanying exophthalmic goiter. If a thyrotoxic goiter is present, ligation of the vessels will frequently modify the symptoms, though this procedure does not result in the marked changes often observed when the goiter is of the exophthalmic type.

The treatment of goiters in the toxic group is definitely surgical, but the results will depend very largely on the method of procedure. It is a well-recognized fact that the exophthalmic goiter should not be operated on during the period of acute exacerbation, and that the steadily increasing intoxication must be arrested before any radical procedure is attempted. It is often necessary to keep these patients in bed for some weeks before attempting any operating at all. Any interference (surgical) undertaken while the symptoms are increasing is liable to result seriously. If the operation is performed during the time the symptoms are decreasing, the result is almost sure to be satisfactory. Patients suffering from thyrotoxic goiter often come for treatment during the period of broken compensation, with marked dilatation of the heart, swelling of the extremities, and even auricular fibrillation. Operations performed in the presence of these conditions are attended with a high mortality. Rest in bed and large doses of digitalis over a considerable period of time will often establish a good compensation and make the patient a very much better surgical risk.

Group IV.—Sarcoma of the thyroid is very rare—we have seen only six cases since 1905. The early stage probably could not be diagnosed except histologically. Even if the malignancy could be recognized clini-

cally, it would be inoperable. Fortunately, carcinoma is also not common. Since 1905 we have seen 105 cases. The basis of a clinical diagnosis of malignancy is usually the hardness of the tumor. If a definite clinical diagnosis of carcinoma can be made, it is then usually inoperable. Often the tumor in the thyroid is small. Its extension into the surrounding tissues results in an early involvement of the recurrent laryngeal nerves, and frequently produces a total loss of voice, which is characteristic in these cases. When the cartilaginous rings of the trachea become infiltrated, there is great difficulty in breathing, at least to a more marked degree than is seen in benign cases. In our experience, even in the cases of malignancy that were not recognized until a histologic section was made, satisfactory operative results have not been obtained. We have operated on a number of patients suffering from cancer of the thyroid who had had the gland resected from five to fourteen years previously for supposedly benign lesions. These patients usually obtained relief after their first operation, and remained well until the definitely malignant tumors appeared in the thyroid. Our experience with carcinoma of the thyroid shows that it is very malignant. I infer that the original operation in these last cases was for benign adenoma and that carcinoma developed in the remaining piece of thyroid tissue.

Frequently a persistent thymus has been present in fatal cases of hyperthyroidism, and for a time it was believed that the interrelationship between the two glands warranted an attempt to remove the thymus at the time of the thyroidectomy. In a few instances we have performed thymectomy in conjunction with the thyroidectomy, but results do not warrant this procedure as a routine. The operation is technically difficult, and there is some question as to what is gained by it.

Features of the Technic.—A great deal has been said regarding the anesthetic which should be employed, and many different views have been expressed. Local anesthesia has been used a great deal and is very satisfactory for small, non-toxic goiters. However, it does not seem that there is any contraindication to the use of a general ether anesthetic in most goiter cases. In our experience the operation is usually performed much more satisfactorily under general etherization. However, there is a good deal of advantage in using a combined anesthetic, *i. e.*, a small amount of 0.5 per cent. novocain injected into the line of incision at the time the patient is being generally anesthetized. With this procedure the operation may begin before the patient is completely anesthetized, and in reality the ether is used only during the operating in the deeper tissues. As soon as the goiter has been removed the ether may be stopped and the operation completed without it, as the superficial tissues have been prepared by the injection of novocain. There will be much

less oozing from the superficial tissues if they have been infiltrated with novocain. We use the combined anesthetic in all our operations on the thyroid. It is important that all nervous patients and those who actually have a damaged heart should be more or less generally etherized. In our experience the operation carries less danger than when it is attempted under a local anesthetic.

The actual technic of thyroid surgery is more difficult than that of surgery in any other region. Experience and improvements in technic have helped a great deal in the control of the blood-vessels during thyroidectomy. In the hyperplastic thyroid all the superficial vessels are dilated; there is oozing from all the smaller vessels, and bleeding is hard to control. But the most serious difficulty arises from the inferior thyroid vessels slipping backward beneath the cervical fascia. If this occurs, the dissection should be made under the fascia and the vessels ligated. If these vessels are not tied, bleeding may continue under the fascia into the mediastinum, and may prove very serious, if not fatal. In a thyroidectomy, even the smallest vessels should be ligated. The slightest oozing afterward may produce a clot, tracheal pressure, and difficulty in breathing. Special attention should be paid to the superficial vessels.

Injury to the trachea, and possibly tracheal collapse during the operation, may add tremendously to the risk of the thyroidectomy. Fortunately, tracheal collapse is not common; it occurs more frequently in cancer cases in which the cartilages have been softened by the extension of the malignancy. Occasionally it occurs when a large adenoma has made considerable pressure on the trachea. Then the fascia over the trachea should be grasped on each side with a hemostat and the collapsed rings pulled apart. Usually, after the lumen has been reëstablished in this way it will be maintained without further difficulty. If the trachea persists in collapsing or has been injured, it may be necessary to make a tracheotomy and keep a tube in place for a few days. Formerly it was considered necessary to dissect the thyroid tissue from the trachea and cartilages as closely as possible, but recently we have found that if we preserve the fascia about the trachea and larynx, and possibly leave some thyroid tissue over the cartilage, the post-operative convalescence is much easier, coughing and irritation are less, and the accumulation of mucus in the trachea and larynx is greatly diminished. This is a very important factor in the technic of thyroidectomy.

Injury to the recurrent laryngeal nerve, though not common, is most exasperating. Our experience has taught us that it is very important

to know the condition of the vocal cords before operating. We are often surprised at the extent of paralysis. It is apparently produced by the goiter and comes on so gradually that the opposite cord may relatively increase its function and the arytenoids continue to approximate. This approximation is to one side rather than in the middle of the larynx. The patient is not aware that any paralysis has occurred, because as long as the arytenoids can be approximated, the speaking and singing voice remains almost normal. Knowledge of the condition of the laryngeal muscles will enable us absolutely to avoid the region of the nerve supplying the muscles that are doing the greater part of the work. If the muscles on one side of the larynx have been greatly inhibited by growth in the thyroid, preservation of the nerve-supply to those on the opposite side will certainly constitute an important feature of the operation. Under these conditions a very slight amount of traumatism to the good recurrent laryngeal nerve might permanently incapacitate it and the patient would be unable to speak. I think that the recurrent laryngeal nerve has almost never been cut, although a number of times it may have been grasped in the hemostat. In the latter instance it will probably recover its function eventually, but the process may be very slow.

In all probability the loss of the voice after goiter operations is frequently due to a change in the position of larynx and trachea resulting from the removal of the thyroid. This is especially true if there has been a great deal of pressure from the growth or edema and swelling in the tissues after operation. Fortunately, the laryngeal muscles seem to have a tendency to hypertrophy and carry the arytenoid on one side across the midline to its opponent, even though the opponent may lie almost motionless on account of the incapacity of the muscle on that side. The restoration of the voice after the recurrent laryngeal nerve has been severed or traumatized I believe is due to this hypertrophy and the increased function in the good cord, rather than to restoration of function in the traumatized side.

There has been considerable discussion as to the amount of thyroid which should be removed. Extirpation of the entire gland will result in serious changes from the loss of thyroid secretion. On the other hand, if a sufficient quantity is not removed, there will be a recurrence of the symptoms. However, it is comforting to know that at least experimental work on animals has shown that if a very small piece of thyroid tissue is retained with its circulation and nerve supply, myxedema will not develop. In our series of cases we have not observed a permanent

post-operative myxedema, and in many instances a very large part of the thyroid has been removed.

Preservation of the posterior capsule, especially since more tissue is being saved posteriorly, has resulted in sparing the parathyroids. Our laboratory workers have diligently examined many thyroids, but have seldom been able to find that the parathyroids were removed with them. We have observed only seven or eight instances of temporary tetany, and this condition apparently resulted from trauma to the parathyroids. In one instance it followed the ligation of both inferior thyroid vessels at one time. This was the most severe case we have seen. Tetany persisted for seven weeks. We controlled the symptoms with calcium lactate. At the end of the seventh week the symptoms subsided and this patient has remained well ever since. In other instances tetany occurred when we least expected it, and when a considerable portion of the posterior part of the thyroid had been saved. Trauma to the circulation or to the nerve supply of the parathyroids is the only basis on which we can explain this condition. In all of these cases the symptoms subsided in a short time—usually a few days.

In conclusion it may be said that at the present time the surgical treatment of lesions of the thyroid rests on a definite clinical and pathologic basis, and that the results more than justify this method of procedure. Most striking results are constantly being obtained by the removal of the goiters producing toxic symptoms.

CHANGES IN THE SUPERIOR CERVICAL SYMPA-
THETIC GANGLIA REMOVED FOR THE RELIEF
OF EXOPHTHALMOS *

LOUIS B. WILSON AND LUIGI DURANTE

The present investigation is based on a study in fixed tissue of the pathologic changes in cervical sympathetic ganglia removed at operation from 16 patients with hyperplastic toxic goiter in the Mayo Clinic, from December 17, 1912, to December 21, 1915, according to the technic described by C. H. Mayo.[22] Within this period sympathectomies were done on 24 patients, but in 8 instances the excised specimen either did not contain ganglionic tissue or the small amount therein was needed for examination in the fresh state. These are not included in the present study.

The questions to be determined are:

1. Are the cervical sympathetic ganglia in hyperplastic toxic goiter a seat of demonstrable histologic changes?

2. If such histologic changes in the cervical sympathetic ganglia exist, is there a relationship between them and the clinical symptoms, on the one hand, and the pathologic changes in the thyroid, on the other?

3. If histologic changes are not demonstrable, is the apparent absence due to faulty technic or to the fact that the sympathetic ganglia have received only impulses, which have left no trace in their structure?

Points in the Normal Anatomy and Histology of the Sympathetic Ganglia of Special Interest in the Present Study.—The superior cervical sympathetic ganglion measures two to three centimeters in length, and four to six millimeters in thickness. The middle cervical ganglion is very much smaller and frequently absent. The superior ganglion is, therefore, more readily excised by the surgeon, and more certain to furnish sufficient material for detailed histologic study.

The two ganglia furnish the entire nerve supply of the thyroid

(Berkeley,[3] Crissafulli,[7] and Rhinehart[27]), both send branches directly
or indirectly to the cardiac plexus; and, through the cavernous plexus,
send fibers to the eye, controlling thus, in part at least, the position of
the eye in its orbit, the width of the palpebral fissure, the width of the
pupil, and accommodation.

In the fetus at term (Fig. 254) the sympathetic ganglia are composed
of three types of cells: (1) The undifferentiated epithelial cells, with a
small amount of cytoplasm and with large nuclei; (2) the stellate cells,
about twice as large as the undifferentiated epithelial cells, with nuclei
and nucleoli, and with short peripheral branching dendrites; and (3)
the adult type of cells. The second type is a transitional form between
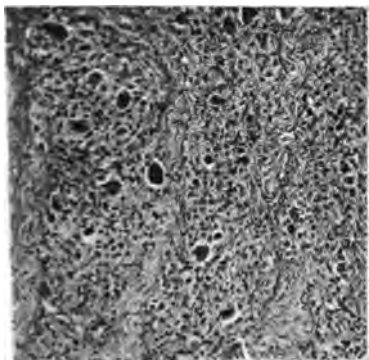
Fig. 254.—(Autopsy 219–15, eight-month fetus.)
Section of superior cervical sympathetic ganglion,
showing three types of normal developing ganglion-
cells. (× 120. Silver impregnation.)
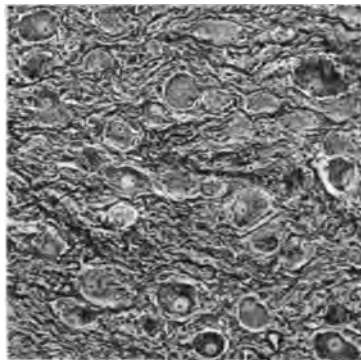
Fig. 255.—(Autopsy 221–15. Female, thirty-
two years of age, mother of fetus shown in Fig. 254.
Death from placenta prævia.) Longitudinal section
of superior cervical sympathetic ganglion, normal ex-
cept for slight hyperchromatization in a few cells.
(× 120. Silver impregnation.)

the first and third types. The ratio of the three types of cells varies in
relation to the age of the embryo; also to some extent in different areas
in the same ganglion. In the normal adult ganglion (Fig. 255) the first
two types of embryonic cells are completely replaced by variations of
the third type.

"The cells of the sympathetic ganglion are always multipolar, with
an axon and several dendrons. Occasionally there are also a number of
short processes confined within the capsule. The cell-body is usually of
an angular form with rounded angles. It is invested by a nucleated mem-
brane sheath, which is continued over the issuing cell processes. The
axon is traceable to its termination as a pale, non-medullated nerve-fiber.
It sometimes, but rarely, becomes thinly medullated. The cells vary
greatly in size, probably in conformity with the length of their axons.

The dendrons rarely extend beyond the confines of the ganglion. They may end by ramifying around their cell-bodies in the ganglion. Fine medullated nerve-fibers, derived from cells in the cord and medulla, enter the sympathetic ganglion, and ramify among the ganglion-cells while their fine terminal fibrils form synapses around the cell-bodies" (Schäfer[28]).

Normally the Nissl bodies stain sharply. They may be scattered uniformly, or they may be arranged in zones about the nucleus. The nuclei are round or oval, often eccentric, with prominent nucleoli and a loose chromatic network. Some cells contain two nuclei. In some of the cells, in an increasing number as age advances, there are found clumps of pigment-granules, yellow or light brown in color. They may be arranged in crescentic masses about the nucleus or in the periphery of the cell.

Histopathology of the Cervical Sympathetic Ganglia in Experimental Lesions and in Severe Toxic and Wasting Diseases.—Tizzoni[29] and others have shown that section, ligation, or cautery of the cervical sympathetic nerve in experimental animals causes degenerative processes both in the ganglion-cells and in the nerve-fibers. The cytoplasm becomes granular at first and later dissolves into round droplets staining black by osmic acid.

Wiener,[35] Floresco,[12] and Missiroli[23] have shown that the thyroid, as well as the ganglia, after section of the cervical sympathetic nerves, shows first a hyperfunction which is quickly followed by degenerative and involutive processes in the cells, causing rapid atrophy of the thyroid.

Hale White in 1887[33] and in 1889[34] examined the superior cervical sympathetic ganglia from 63 non-goitrous patients coming to autopsy, and from 69 other mammals, including monkeys, carnivora, etc. From this study he concluded that in the lower mammals, and in young humans, the ganglia are functionally active, and that in monkeys there are evidences of the commencing loss of function, which in man, though maintained well into adult life, begins to disappear in old age. Vas[31] and others have reviewed White's work, and while the frequency of the changes in the cervical sympathetic ganglia of the aged is agreed upon, most observers ascribe them to arteriosclerosis or to severe toxic or wasting disease, factors which were present in White's cases occurring in adults.

Previous Observations on the Pathology of the Cervical Sympathetic Ganglia in Cases of Hyperplastic Toxic (Exophthalmic) Goiter.—Eulen-

berg and Guttmann,[11] in 1869, reported the examination of cervical ganglia from 12 cases of Basedow's disease, as then diagnosed, with the finding of only unimportant lesions. Following this, a number of other observers, using only general histologic technic, made examinations of the cervical ganglia from scattered cases of more or less accurately diagnosed Basedow's disease. Möbius,[24] however, in 1896, summarized the previous observations somewhat ironically, thus:

"The ganglion was too large or too small. The nerve was too thick or too thin. There is too much connective tissue or too few nerve-cells. The nerve-cells are deformed or shrunken. There are small hemorrhages and destruction of nerve-fibers."

Bonne[4] reported the examination of a superior cervical sympathetic ganglion resected by Jaboulay,[17] in 1897, from a woman forty-seven years of age whose goiter had begun twenty-two years previously. He concluded that the changes, except for the presence of pigment grains scattered throughout the connective tissue, might be attributed to abnormal involution.

Graupner,[13] in 1898, reported the examination of the superior cervical sympathetic ganglia removed at necropsy from a female patient with the characteristic symptoms of Basedow's disease. He considered the changes in the ganglion-cells unimportant, though noting unduly dilated cell capsules some of which contained only a dark-colored mass, while other cell-capsules were dwarfed and contained strongly pigmented ganglion-cells. He reported also a second case of doubtful Basedow's disease in a woman thirty-eight years of age who had an enlarged thyroid for eight years. He concluded that the sympathetic ganglion was entirely normal.

Herbet,[14] in his thesis in 1900, reported without details the histologic examination by Pilliet of a superior cervical sympathetic ganglion removed at operation from a patient who had had exophthalmic goiter for three years. Nothing definite was found.

Wood,[39] in 1904, reported without clinical details the examination of nine ganglia removed from patients with exophthalmic goiter, as follows:

"1. There is no definite increase in the connective tissue of the ganglia. 2. Pigmentation of the ganglion-cells is quite constant and abundant, though not present in all the cells. 3. A small proportion, always less than half, of the ganglion-cells shows a central chromatolysis when stained by Nissl's method. In some cells the changes are advanced and no chromophilic bodies could be seen. In others they were clustered

about the periphery of the cell. The nuclei were often eccentric in the degenerated cells. 4. No fiber degeneration could be demonstrated. All the ganglia showed about the same changes. Control ganglia from autopsy cases dying from a variety of diseases did not show marked chromatolysis. An occasional cell with degeneration could be seen. The amount of pigment formed was variable in these controls. It was more abundant in the aged than in the adults. Certain amounts seem to be present in some of the ganglion-cells of the sympathetic, at least in some cases which I have been able to examine."

Horand, in 1910,[15] reported the examination of the ganglia from one patient, and in 1911[16] the examination of the ganglia from two more patients, all three of whom had been operated on by Jaboulay.

"Case 1: Male, aged nineteen years, exophthalmic goiter for two years. Histologic examination after mercury nitrate fixation and hematoxylin staining showed nerve-cells reduced in number, pigmented, degenerated, atrophic, and compressed in the proliferating connective tissue. Case 2: Male, aged thirty-two years, exophthalmic goiter for four years. Case 3: Female, aged thirty-eight years, exophthalmic goiter for ten months."

Horand described the lesions of the ganglia from Cases 2 and 3 together, in abstract, as follows:

"Ganglia fixed in Bouin's fluid, and stained with hematoxylin-eosin. Nerve-cells reduced in number, pigmented, atrophic. In later stages cell may be transformed into black, melanin-like patch. Pigment may also be disseminated through surrounding cellular tissue near capillaries and veins. There are perivascularitis and marked increase of connective tissue through ganglion."

Aoyagi[1] examined specimens removed postmortem from two patients and reported as follows:

"Case 1: Male, aged forty-one years, partial paralysis seven years previously. Four years ago physician diagnosed struma and exophthalmos. On admission to hospital exophthalmos light grade, struma plain, heart action somewhat increased, irregular. Autopsy three and one-half hours after death. Cells vacuolated, irregular in outline, often shriveled, and sometimes disappeared. A deposit of pigment in a few cells, but never above the normal."

"Case 2: Male, aged twenty-eight years, hyperhidrosis five months, palpitation three and one-half months, goiter three months, exophthalmos one and one-half months. Autopsy ten hours after death. Microscopic picture same as in Case 1. In the tissues examined by Bielschowsky's method the cell-body shows a diffuse, blackish impregnation or saturation. The nuclei may be irregular or absent."

The diagnosis of exophthalmic goiter in Aoyagi's first case may be questioned. In both cases there is suspicion that the vacuolation of the nerve-cells may have been due to postmortem autolysis.

Summary of Preceding Observations.—A careful analysis of the preceding observations shows that the examination of sympathetic ganglia removed at necropsy is apt to be misleading, unless careful note is made of the clinical details of preceding toxic or chronic wasting disease, of the presence of general arteriosclerosis, and especially of the possibility of postmortem autolysis. Ganglia removed more than four hours, or in septic cases two hours, after death, except under most favorable mortuary conditions, are almost certain to show autolytic changes. Material from surgical operations, properly fixed, should be least misleading. It is to be regretted that more detailed examinations by modern technic have not been reported on ganglia from this source.

Trousseau,[30] in 1860, suggested that disease of the cervical sympathetic was a factor in exophthalmic goiter, and that operative measures on the ganglia should be taken to relieve exophthalmos. Bénard,[2] in 1882, showed that stimulation of the cervical sympathetic caused protrusion of the eyeball and prevented closure of the lids. It was not, however, until 1896 that an operation removing the cervical sympathetic ganglia or nerves was first done by Jaboulay.[17] Following him Jonnesco,[18] Kocher,[19] Mayo,[22] and many other surgeons have repeatedly excised portions of the cervical sympathetic ganglia or nerves for the relief of exophthalmic goiter or of exophthalmos alone.

Material for the Present Study.—The 20 ganglia constituting the material on which the present study is based were removed at operation from 16 patients with hyperplastic toxic goiter. From 2 of these patients the right superior ganglion only was removed, from 3 the left superior only, and from 11 both right and left superior ganglia were removed. In 5 instances the right or left, or both the right and left, middle superior ganglia were also removed. Small pieces of ganglia were examined in frozen sections of the fresh tissue immediately after operation by the method described by Wilson.[36, 37] The remainder of the specimen, or specimens, was fixed in 10 per cent. formalin, and reserved for subsequent examination. In all, 35 ganglia from 24 patients have been examined, either in sections of fresh tissue or in sections of fixed tissue.

Technic of Examination of Fixed Tissue.—Each ganglion was divided transversely into equal parts. One, the superior part, which contained the majority of the afferent and efferent branches, was further sub-

divided longitudinally into two parts. One of these was used for silver-nitrate impregnation, and the other for Flemming's strong solution. The inferior part was divided transversely into small segments of a few millimeters each. Some of these were used for staining with hematoxylin and eosin; some with Weigert-van Gieson for connective tissue; some with Weigert-Luden[21] for myelin; some with Held-Nissl for distribution of chromatin; some for specific fat, iron, and pigment reactions; and some for silver-nitrate impregnation. All preparations were examined in serial paraffin sections except those cut frozen for the study of pigment.

The silver-nitrate impregnation, with subsequent reduction by pyrogallic acid, as used by Ramón y Cajal[26] and Levaditi[20] for the study of endocellular reticulum and the dendrites of cerebral and spinal ganglion-cells, was employed by us for the study of sympathetic ganglia with very satisfactory results. The details of intracellular structure and the dendrites, furnished by this method, are comparable with those obtained in experimental neurology with Ehrlich's methylene-blue vital stain.

ABSTRACTS OF CLINICAL AND PATHOLOGIC PROTOCOLS

(Arranged in order of the duration of symptoms. All degrees of symptoms, pathologic changes, etc., not capable of being stated in other more accurate terms, are indicated by the figures 0, 1, 2, 3, 4, 5, in which 5 indicates the greatest or most severe change.)

CASE 1 (A-107,215).—The patient was a female, twenty-four years of age, who had had an enlarged thyroid for ten months and well-defined symptoms of hyperplastic toxic goiter for four months. The degree of exophthalmos was 1 in each eye. A left sympathectomy, with ligation of the superior thyroid arteries on both sides, was done, and four months later the right lobe, isthmus, and two-thirds of the left lobe of the thyroid were extirpated.

Histologic examination of the left superior sympathetic ganglion (Fig. 256) showed hyperpigmentation and granular degeneration of the ganglion-cells, general, diffuse, and intense, 5; atrophy of the ganglion-cells, 4; diminution in the number of ganglion-cells, 3; increase of perivascular connective tissue, 1; and increase of connective tissue throughout the ganglion, 2. Examination of the thyroid showed advanced parenchymatous hypertrophy and hyperplasia, Type B[38] (Fig. 257), despite the ligation of the thyroid vessels four months previously.

CASE 2 (A-129,966).—The patient was a female, thirty years of age, who had noticed enlargement of her thyroid one month previously, and severe symptoms of hyperplastic toxic goiter beginning one year previously. The degree of exophthalmos was graded 3 in each eye. A left sympathectomy, with ligation of the left superior thyroid vessels, fol-

lowed three months later by a double resection of all but the posterior part of each lobe of the thyroid, was done.

Histologic examination of the left superior sympathetic ganglion (Fig. 258) showed hyperpigmentation and granular degeneration of the
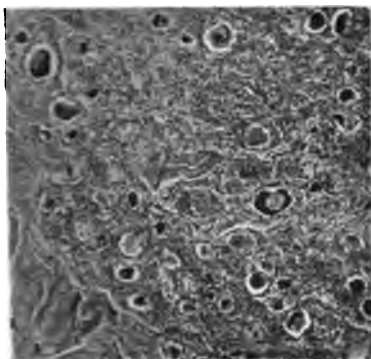
Fig. 256.—Case 1 (A-107,215. Female, twenty-four years of age. Enlarged thyroid eleven months, and symptoms of hyperthyroidism five months before sympathectomy). Longitudinal section of superior cervical sympathetic ganglion, showing the total number of cells not apparently reduced, a few only hyperchromatic, and many in varying stages of granular degeneration. (X 120. Silver impregnation.)
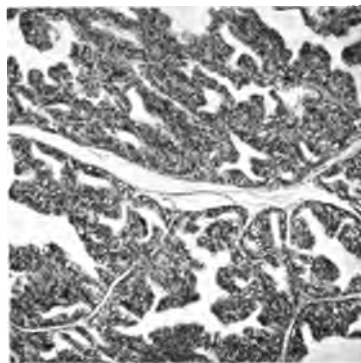
Fig. 257.—Case 1 (A-107,215). Section of thyroid removed four months after removal of sympathetic ganglion shown in Fig. 256, showing active parenchymatous hypertrophy and hyperplasia, type B. (X 60. Hematoxylin-eosin.)
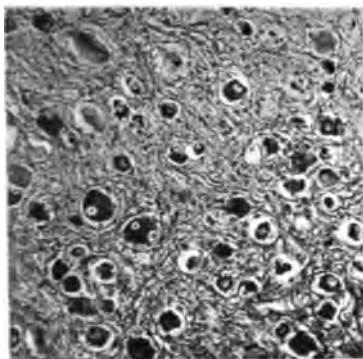
Fig. 258.—Case 2 (A-129,966. Female, thirty years of age. Enlarged thyroid one month, symptoms of hyperthyroidism one year). Section of superior sympathetic ganglion; condition similar to that shown in Fig. 256. (X 120. Silver impregnation.)
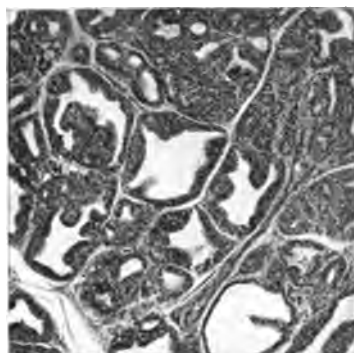
Fig. 259.—Case 2 (A-129,966). Section of thyroid removed three months after removal of ganglion shown in Fig. 258, showing acute parenchymatous hypertrophy and hyperplasia, type B. (X 60. Hematoxylin-eosin.)

ganglion-cells, diffuse and intense, 5; atrophy of the ganglion-cells, 4; increase of perivascular connective tissue, 2. Examination of the left lobe of the thyroid, which was removed three months after ligation of the superior thyroid vessels, showed advanced parenchymatous hypertrophy and hyperplasia, Type B [38] (Fig. 259).

CASE 3 (A-106,349).—The patient was a female, twenty-three years of age, who first noticed enlargement of her thyroid, with severe symptoms of hyperplastic toxic goiter, one year previously. The degree of exophthalmos was graded 2 in the right eye and 3 in the left. The right and left superior cervical sympathetic ganglia, with a portion of the left middle ganglion, were removed, and the superior thyroid vessels on both sides ligated.

Histologic examination of the left superior cervical ganglion showed hyperpigmentation and granular degeneration of the ganglion-cells, 3; atrophy of the ganglion-cells, 2; diminution in the number of ganglion-cells, 3; increase of connective tissue throughout the ganglion, 3; and a diffuse inflammatory process in the ganglion.

CASE 4 (A-75,687).—The patient was a male, forty-four years of age, who at the time of examination had had symptoms of hyperplastic toxic goiter for nine months. The degree of exophthalmos was graded 3 in each eye. The right superior thyroid vessels were ligated, and a week later the right lobe and isthmus of the thyroid were extirpated. Eighteen months later, or two years and three months after the onset of symptoms, the exophthalmos had increased to a degree graded 4, and the superior cervical sympathetic ganglia on both sides were removed.

The superior sympathetic ganglion from the right side only was examined by the silver-impregnation method, and showed hyperpigmentation and granular degeneration, general, diffuse, and intense, 5; atrophy of the ganglion-cells, 3; and increase of perivascular connective tissue, 4. Examination of the thyroid showed early regressing parenchymatous hypertrophy and hyperplasia, Type C1.[38]

CASE 5 (A-124,585).—The patient was a female, thirty-two years of age, who had had an enlargement of the thyroid for ten years, but with no apparent symptoms until two years before, when sad news prostrated her, causing vomiting, diarrhea, and loss of weight and strength, followed by exophthalmos. Two similar attacks from similar causes subsequently occurred. At the time of operation her exophthalmos was graded 1 in the right eye and 2 in the left. A left cervical sympathectomy was done, with ligation of the left and right superior thyroid vessels, followed four months later by removal of the right lobe of the thyroid.

Histologic examination of the left superior sympathetic ganglion showed diffuse granular degeneration of the cells, 3; hyperpigmentation, 1; cells of embryonic type, 3; atrophy of the ganglion-cells, 3; diminution in the number of the ganglion-cells, 3; and increase of connective tissue throughout the ganglion, 2. Examination of the thyroid showed very advanced regression of an old parenchymatous hypertrophy and hyperplasia, Type C 3,[38] with marked increase of the lymphoid tissue.

CASE 6 (A-76,891).—The patient was a female, twenty-two years of age, who had had an enlarged thyroid and severe symptoms of hyper-

plastic toxic goiter for two years. At the time of examination her exophthalmos was graded 1 in each eye. The superior cervical sympathetic ganglia on both sides were removed, and the superior thyroid vessels ligated. One year and eight months later both lobes of the thyroid were injected with boiling water, and subsequently the right lobe and isthmus and two-thirds of the left lobe were extirpated.

Histologic examination of the left superior cervical ganglion showed hyperpigmentation and granular degeneration, moderate, 2; in some areas many ganglion-cells normal; diminution in the number of cells, 2; atrophy of the ganglion-cells, 2; and increase of connective tissue, 2. Examination of the thyroid showed destruction of the parenchyma in some areas from injections of boiling water made fifteen and eleven days before the thyroidectomy. Near these areas regeneration had begun. Elsewhere there was abundant advanced parenchymatous hypertrophy and hyperplasia, Type B.[38]

CASE 7 (A-99,174).—The patient was a female, forty-four years of age, who, two years previously, had noticed that she had a full neck and that her eyes protruded, though none of the other symptoms of hyperplastic toxic goiter were present at any time. At the time of examination the degree of exophthalmos was graded 1 in each eye, and Stellwag's symptom 3 in each eye. Both superior cervical sympathetic ganglia were removed.

Histologic examination of the right superior sympathetic ganglion showed hyperpigmentation and granular degeneration of the ganglion-cells, 2; atrophy of the ganglion-cells, 2; diminution in the number of the ganglion-cells, 2; and increase in connective tissue throughout the ganglion, 4.

CASE 8 (A-49,068).—The patient was a female, thirty-four years of age, who dated her symptoms of hyperplastic toxic goiter at a period two weeks previous to a supposed miscarriage, which occurred one year before. The right lobe and isthmus of the thyroid and a small cyst from the left lobe were extirpated. The patient remained in good health for nearly two years, when attacks of orbital headaches, accompanied by nausea, and lasting from one to four days, developed. When reëxamined, the degree of exophthalmos was graded 4 in the right eye and 2 in the left. Two years and two months after her first operation, or three years and two months after the onset of symptoms, the right superior and middle cervical sympathetic ganglia were removed.

Histologic examination of the right superior ganglion (Fig. 260) showed hyperpigmentation and granular degeneration of the ganglion-cells, diffuse and intense, 5; cells of embryonic type, 1; atrophy of the ganglion-cells, 2; diminution in the number of ganglion-cells, 3; and increase of connective tissue throughout the ganglion, 2. The very great diminution in the number of functionating cells in this ganglion was no doubt due, in part, to the previous removal of the thyroid. Examination

of the thyroid showed advanced regression of parenchymatous hypertrophy and hyperplasia, Type C2[38] (Fig. 261).

CASE 9 (A-112,424).—The patient was a female, thirty-three years of age, who, after an indeterminate period of exophthalmic goiter, had had a partial thyroidectomy done elsewhere two years previously. At the time of examination the degree of exophthalmos was graded 3 in each eye. The right and left superior cervical sympathetic ganglia were removed.

Histologic examination of the right superior cervical ganglion showed hyperpigmentation and granular degeneration of the ganglion-cells, 1; embryonic cells, 1; atrophy of the ganglion-cells, 3; diminution in the
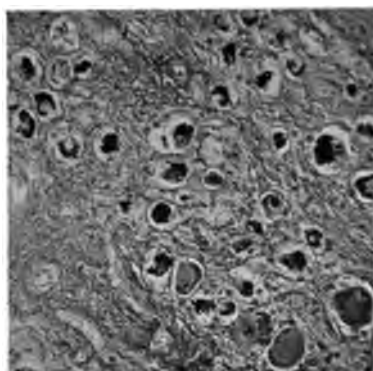
Fig. 260.—Case 8 (A-49,068. Female, thirty-four years of age. Enlarged thyroid and symptoms of hyperthyroidism three years before sympathectomy). Cross-section of superior cervical ganglion, showing the total number of cells reduced, many showing only as small masses of pigment in shrunken cell-capsules. The extensive destruction is probably due in part to the removal of the thyroid two years before sympathectomy. (× 120. Silver impregnation.)
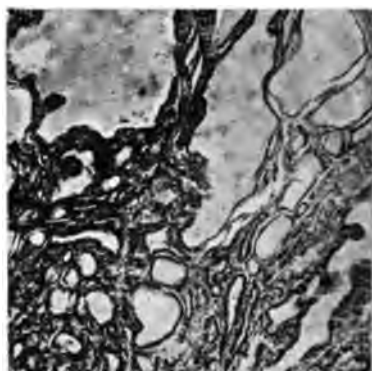
Fig. 261.—Case 8 (A-49,068). Section of thyroid removed two years before the removal of the ganglion shown in Fig. 260, showing that even at that time considerable regression of the hypertrophy and hyperplasia had occurred—Type C2. (× 60. Hematoxylin-eosin.)

number of ganglion-cells, 3; and increase of connective tissue throughout the ganglion, 2.

CASE 10 (A-118,918).—The patient was a female, twenty-four years of age, who had had enlargement of the thyroid and severe symptoms of hyperplastic toxic goiter for three years, beginning with a fall on the ice. At the time of examination the exophthalmos was graded 4 in the right eye and 3 in the left. The right and left superior and middle cervical sympathetic ganglia were removed, and the right and left superior thyroid vessels ligated. Six months later the right lobe and isthmus of the thyroid were extirpated.

Histologic examination of the right superior cervical ganglion (Fig. 262) showed granular degeneration, 3; hyperpigmentation, 2; embryonic cells, 1; atrophy of the ganglion-cells, 1; diminution in the number of

ganglion-cells, 3; and increase of connective tissue in the ganglion, 1. Examination of the thyroid showed advanced regression of primary parenchymatous hypertrophy and hyperplasia, Type C2[38] (Fig. 263).

CASE 11 (A-139,018).—The patient was a female, twenty-seven years of age, the enlargement of whose thyroid and symptoms of hyperplastic toxic goiter had begun three years and six months previously. Two months after the onset of her symptoms she had had a resection of the right lobe of her thyroid elsewhere. Her eyes had never improved, though otherwise she had remained subjectively well for two years. During the last year her symptoms of hyperplastic toxic goiter had increased. At the time of examination the degree of exophthalmos in each eye was graded 3. The right and left superior and middle cervical sympathetic
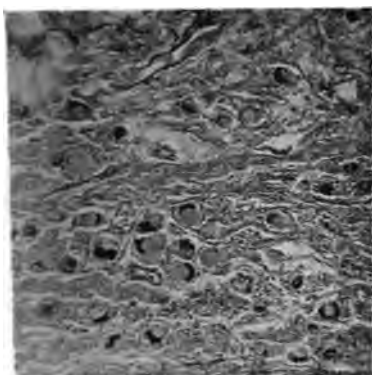
Fig. 262.—Case 10 (A-118,918. Female, twenty-four years of age. Enlarged thyroid with symptoms of hyperthyroidism, three years before sympathectomy). Longitudinal section of superior cervical sympathetic ganglion showing reduction in the total number of cells, those remaining degenerated, but not to such an extent as many shown in previous figures, thus indicating complete destruction of many of the cells with partial recuperation of a few. (× 120. Silver impregnation.)
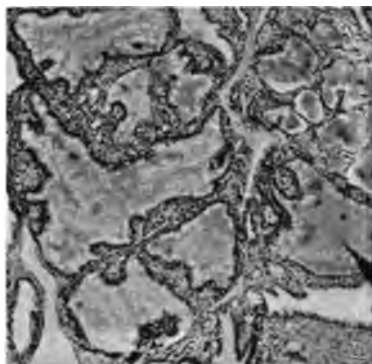
Fig. 263.—Case 10 (A-118,918). Section of thyroid removed six months after removal of ganglion shown in Fig. 262, shows early regression of parenchymatous hypertrophy and hyperplasia—Type C1. (× 60. Hematoxylin-eosin.)

ganglia were removed, and the right and left superior thyroid vessels ligated.

Histologic examination of the right superior cervical ganglion showed hyperpigmentation and granular degeneration, 2; atrophy of the ganglion-cells, 1; diminution in the number of ganglion-cells, 3; and increase in connective tissue throughout the ganglion, 1. Examination of the left superior ganglion showed hyperpigmentation and granular degeneration, 1; atrophy of the ganglion-cells, 1; diminution in the number of ganglion-cells, 1; and increase of connective tissue throughout the ganglion, 1.

CASE 12 (A-132,122).—The patient was a female, twenty-six years of age. Her symptoms of hyperplastic toxic goiter had begun five years previously, following desertion by her husband. During the last nine

months she had been gaining steadily in health, and exophthalmos was the only symptom causing her to seek surgical aid. At the time of examination the exophthalmos was graded ˙3 in each eye. The right and left superior and middle cervical sympathetic ganglia were removed, and the right and left superior thyroid vessels ligated.

Histologic examination of the right superior sympathetic ganglion showed hyperpigmentation and granular degeneration, 2; embryonic cells, 1; atrophy of the ganglion-cells, 2; diminution in the number of the ganglion-cells, 4; and increase of connective tissue throughout the ganglion, 3.

CASE 13 (A–134,568).—The patient was a female, twenty-two years of age, who, six months after acute suppurative appendicitis, five years previously, developed severe symptoms of hyperplastic toxic goiter, which continued for nine months, when they were relieved by a double ligation of the thyroid arteries elsewhere. The patient had had no symptoms during the last year. At the time of examination the degree of exophthalmos was graded 4 in the right eye and 2 in the left. The right superior cervical sympathetic ganglion was removed.

Histologic examination of the ganglion showed granular degeneration of the ganglion-cells, 3; hyperpigmentation, 1; embryonic cells, 1; atrophy of the ganglion-cells, 3; diminution in the number of ganglion-cells, 2; and increase of connective tissue in the ganglion, 1.

CASE 14 (A–119,713).—The patient was a female, forty-eight years of age, the enlargement of whose thyroid and symptoms of hyperplastic toxic goiter developed five years previously. Following medicinal treatment, she had greatly improved in health for the past three years, except that her eyes were more prominent than before. At the time of examination the exophthalmos was graded 4 in each eye. The right and left superior cervical sympathetic ganglia were removed, and the right and left superior thyroid vessels ligated.

Histologic examination of the right superior ganglion showed hyperpigmentation and granular degeneration of the ganglion-cells, 4; atrophy of the ganglion-cells, 3; diminution in the number of ganglion-cells, 1; and increase of connective tissue throughout the ganglion, 1. Examination of the left superior ganglion showed hyperpigmentation and granular degeneration of the ganglion-cells, 4; atrophy of the ganglion-cells, 2; diminution in the number of ganglion-cells, 2; and increase of connective tissue throughout the ganglion, 2.

CASE 15 (A–53,650).—This patient was a female, twenty-one years of age, the enlargement of whose thyroid and symptoms of hyperplastic toxic goiter had begun one year previous to examination. At that time her exophthalmos was graded 4 in each eye. The right and left superior thyroid vessels were ligated, and four months later the right lobe of the thyroid was extirpated. Three years and eight months later, or four

years and eight months after the onset of her symptoms, the right and left superior cervical sympathetic ganglia were removed.

Histologic examination of the left superior cervical ganglion (Fig. 264) showed hyperpigmentation and granular degeneration of the ganglion-cells, 1; embryonic cells, 1; atrophy of the ganglion-cells, 2; diminution in the number of ganglion-cells, 4; increase of perivascular connective tissue, 2; and increase of connective tissue throughout the ganglion, 3. Examination of the thyroid showed very advanced regression of primary parenchymatous hypertrophy and hyperplasia, Type C3[38] (Fig. 265).

CASE 16 (A–119,243).—The patient was a female, thirty-seven years of age, who, eleven years previously, had noticed enlargement of her
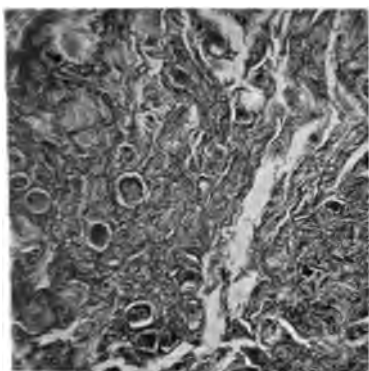
Fig. 264.—Case 15 (A–53,650. Female, seventeen years of age. Enlarged thyroid and symptoms of hyperthyroidism for five years). Longitudinal section of left superior cervical ganglion showing apparent reduction in the total number of cells, but a few of those present in fairly good condition. (× 120. Silver impregnation.)
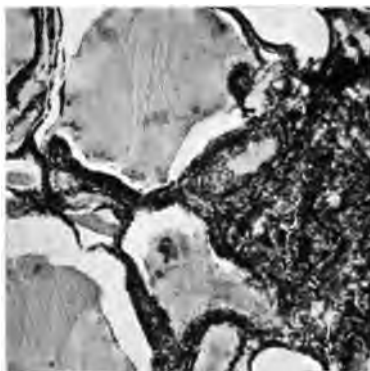
Fig. 265.—Case 15 (A–53,650). Section of right lobe of thyroid removed four months after ligation of right superior thyroid vessels, showing very advanced regression of parenchymatous hypertrophy and hyperplasia—Type C3. (× 60. Hematoxylin-eosin.)

thyroid and well-defined symptoms of hyperplastic toxic goiter, which continued for over two years and then gradually subsided. At the time of examination the exophthalmos was graded 0 in the right eye and 4 in the left, while Stellwag's symptom was graded 4 in the right eye and 0 in the left. The right and left superior cervical sympathetic ganglia were removed, and the right and left superior thyroid vessels ligated.

Histologic examination of the right superior cervical ganglion showed hyperpigmentation and granular degeneration of the ganglion-cells, 1; atrophy of the ganglion-cells, 2; reduction in the number of ganglion-cells, 4; increase of connective tissue in the ganglion, 3; and inflammation of the ganglion, 2.

Summary of Protocols.—A study of the preceding abstracts of protocols shows that 13 of the patients were females between twenty-one and

thirty-seven years of age, two were females forty-four and forty-eight years of age, and one was a male forty-six years of age. Thus it will be seen that only three of the patients (Nos. 4, 7, and 14) were adults in whom changes in the sympathetic ganglia, due to senility alone, might possibly have begun. These three patients (No. 4, a male of forty-six years of age; No. 7, a female, forty-four years of age; and No. 14, a female, forty-eight years of age) showed very little diminution in the total number of cells in the ganglion, though Nos. 4 and 14 showed very marked hyperpigmentation and granular degeneration of the cells present. Patient No. 4 was very neurotic, but clinically did not appear to have a high degree of intoxication. Patient No. 7 had had no toxic symptoms at any time. There is a possible relationship between the extreme general increase of connective tissue in the ganglion and the exoph-thalmos and Stellwag's symptom, which were the only complaints. Patient No. 14 had passed her period of maximum severity of toxic con-ditions five years before sympathectomy was done, her symptoms at the time of operation being those of slight remaining hyperthyroidism, with a general appearance of developing myxedema.

Of the remaining 13 patients, ages twenty-one to thirty-seven years, 5 (Nos. 1, 2, 3, 4, and 6) may be considered as having active hyperplastic toxic goiter. In 4 of these 5 cases there were a very marked hyperpig-mentation, granular degeneration, and atrophy of the ganglion-cells. In the other case (No. 6) the symptoms, though acute at the beginning, were mild throughout. Similarly the changes in the sympathetic ganglia were of moderate degree.

Cases Nos. 8, 10, and 11 were cases in which a considerable regression of the clinical symptoms had occurred. In Case No. 8 the degree of hyperpigmentation and granular degeneration was very marked. In Cases Nos. 10 and 11 it was relatively small, though a considerable diminution in the number of cells in the ganglia had occurred in both instances.

Cases Nos. 5, 9, 12, 13, 15, and 16 showed a very marked regression or complete absence of toxic symptoms. In the ganglia from these patients the hyperpigmentation and granular degeneration of the cells present was very slight, while the diminution in the number of cells was most marked.

Thus it will be seen that the degree of hyperpigmentation, granular degeneration, atrophy, and reduction in the number of cells was in direct ratio to the continuance of symptoms of hyperthyroidism. The increased

amount of perivascular connective tissue and connective-tissue stroma generally throughout the gland was similarly in direct ratio to the time during which symptoms of hyperthyroidism had continued. In only one (No. 3) of the ganglia was there marked evidence of acute inflammation, though the marked sclerosis in Case No. 7 may have been due to a chronic inflammatory process. The increase of connective tissue in the ganglia from the chronic cases may be interpreted as due to the irritation from inflammation, or as merely a replacement following the destruction of the ganglionic nerve-cells. In only two cases (Nos. 7 and 9) were the ganglia markedly increased in size. It is interesting to note that in neither of these cases was there marked evidence of thyrotoxicosis at the time of sympathectomy. In the majority of the cases, at the time of operation it was noted that the ganglia were intimately connected by firm adhesions to the surrounding tissue.

Fig. 266.—Case 8 (A–49,068). Ganglion-cell showing advanced chromatolysis with slight lipochrome hyperpigmentation in periphery around it, and remnants of other ganglion-cells with advanced granular degeneration near by. (× 600. Silver impregnation.)

Hyperchromatization, Chromatolysis, and Hyperpigmentation.—Hyperchromatization was not a marked characteristic of the ganglion-cells examined. Chromatolysis, however, was very marked, as was best shown by the Nissl preparations, though readily recognized in silver impregnations (Fig. 266). Extensive chromatolysis proceeding to the stage of complete disappearance of the cell outlines in Nissl preparations, which has been studied in extenso by Dolley [8, 9, 10] and other observers, is only a part of a process herein designated "granular degeneration."

The nature, origin, and biologic significance of the pigment of nerve-cells still remain a matter of discussion (Neumann[25]). In the ganglion-cells of the cerebrospinal axis and of the sympathetic system there have been described two kinds of pigment, both of apparently autogenous origin, i. e., produced by normal cell metabolism. The first of these is brown in unstained preparations, and is no doubt melanin. The second is a substance which, in unstained preparations, is yellow, but stains black with osmic acid and silver solutions, and belongs to the lipochromes. The quantity of pigment increases with advancing age or, in other words,

with the age of the cell, since the ganglionic cells are probably without regenerative power in adult life.

In pathologic conditions, as shown by our observations, the increased pigment is distributed irregularly throughout the cell-body. It is found both in cells in which the cytoplasm is apparently normal and in cells in which varying degrees of granular degeneration of the cytoplasm is present (Fig. 266). The pigment is stained slightly reddish-brown by Sudan III, by osmic acid, and by silver-nitrate impregnations. It is distinguished from the remainder of the cytoplasm by staining much more deeply. This is in contrast with the granules which come from the
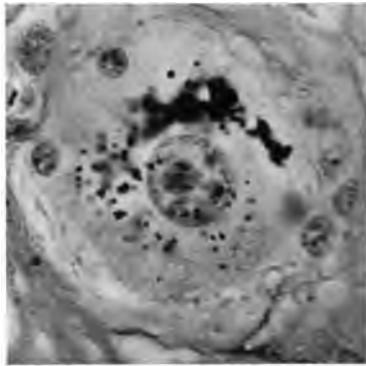
Fig. 267.—Case 2 (A–129,966). Ganglion-cell with granular degeneration of the protoplasm and nucleus in early stage of karyolysis. (× 600. Silver impregnation.)
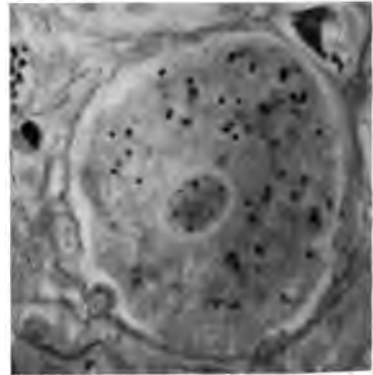
Fig. 268.—Case 2 (A–129,966). Hydropic ganglion-cell in early stage of granular degeneration near an atrophic ganglion-cell in an advanced stage of granular degeneration. (× 600. Silver impregnation.)

destruction of protoplasm and which are stained intensely red with Sudan III, and black with osmic acid and silver nitrate.

While it is difficult to determine the exact pathologic significance of hyperpigmentation, it appears probable that the process is associated with the earlier stages of granular degeneration. When it exists alone in a cell, it cannot be taken as a conclusive sign of degeneration.

Granular Degeneration.—By "granular degeneration" we mean decomposition of the cytoplasm and its subsequent transformation into spheric drops. It is probable that the first stage of granular degeneration is hyperchromatization with the aggregation of the chromatin granules around the nucleus. The second stage is one of hydropic degeneration in which the chromatin granules disappear (chromatolysis). The third stage of granular degeneration consists in a partial destruction of

the cytoplasm and beginning disintegration of the nucleus (Fig. 267). The fourth stage marks the total destruction of the cytoplasm with a partial destruction of the nucleus (Figs. 268 and 269). In the fifth stage there is complete destruction and transformation of the cell-body into small spheric granules, collected in the lymphatic capsular space (Fig. 270). This space, though usually small, is sometimes very large, since it may continue to outline the contour of the degenerating hydropic cell. The granules of the degenerating protoplasm are stained intensely red by Sudan III, blue by Weigert-Luden's method,[21] and deeply black by Flemming's solution and silver-nitrate impregnations. They do not give an iron reaction. They are probably of the nature of myelinic fat.
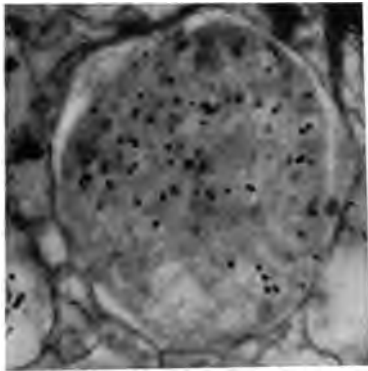
Fig. 269.—Case 8 (A-49,068). Hydropic ganglion-cell in early stage of granular degeneration with complete disappearance of the nucleus. (× 600. Silver impregnation.)
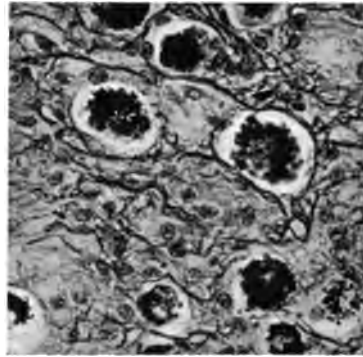
Fig. 270.—Case 8 (A-49,068). Shrunken ganglion-cells in various stages of advanced granular degeneration. (× 400. Silver impregnation.)

Myelinic degeneration is the more common form in the ganglion-cells and nerve-fibers. Myelin is with great difficulty differentiated in the tissue from fat by chemical means. Microchemical reactions are of some, but not of conclusive, value. Both myelin and fat reduce osmic acid and are stained red with Sudan III. With the Weigert-Luden stain and with silver-nitrate impregnation we can approximately differentiate between myelin and fat, since by the former method the myelin is stained blue and the fat is left unstained, while with silver nitrate only the myelin precipitates the silver. In addition, the Marchi-Algeri method, based upon the fact that osmic acid does not stain myelin in tissues fixed for two or three months in Müller's fluid, but does stain the fat in tissues similarly fixed, gives corroborative results.

Atrophy of the Ganglion-cells.—The atrophy of the ganglion-cells is characterized by a notable diminution in size, sometimes to one-fourth the normal diameter, and by eccentric deformities of the cell-body. In areas in which the proliferation of the connective tissue is intense, the atrophy of the ganglion-cells is most marked. The cells assume an irregular stellate appearance with the nucleus in the periphery and with lipochrome pigment diffused throughout the protoplasm, which stains more intensely than normal. Usually the capsule of the cell contracts so that the atrophied cell completely fills it (Fig. 270). The lining cells of the capsule are often increased in number. The network of nerve-fibers surrounding the cell in its lymph-space is rarely visible.

Fig. 271.—Case 4 (A-75,687). Oblique section through periphery of ganglion, showing marked increase of perivascular connective tissue and granular degeneration of ganglion-cells. (X 60. Silver impregnation.)

Embryonic Cells.—It is difficult to differentiate embryonic ganglion-cells from atrophic ganglion-cells. It is improbable that in the normal adult ganglion any embryonic cells exist. Yet certain it is that in some of the adult ganglia in this series, in which active degenerative processes have long been quiescent, there exist cells that are indistinguishable from the typical embryonic nerve-cells in the ganglia of the fetus.

Nerve-fibers in the Ganglia.—In Case No. 12 we found some evidence of an increase of the myelin fibers. This is probably due to the fact that the proliferating connective tissue is sometimes so arranged as to cause the compression of nerve-fibers, instead of their suppression.

In Case No. 4 the myelinic sheath of the nerve-fibers was broken into fragments, which appeared as spheric drops readily demonstrable by Flemming's and Weigert-Luden's methods of staining.

In cases in which the degeneration of the ganglion-cells was advanced the fine spiral fibers which are wrapped about the ganglion-cell normally could not be found. It is probable that the myelinic granular decomposition coming from the destruction of the cell-body is accompanied by a similar degeneration in the terminal spiral fibers.

Blood-vessels.—It was difficult to judge in most instances whether there was an increase or a diminution of the blood-vessels in a given

ganglion. The wide limits of the normal distribution of the vessels, and the variations in different parts of the same ganglion, prevented positive determination, except in those cases in which the increase or diminution was very prominent.

Thickening in the walls of the vessels always occurred in the external and middle coats (Fig. 271). We have observed no lesions of the intima. The change in the external layer of both large and small vessels consists of an increase of perivascular connective tissue, which is sometimes very marked.

The proliferated perivascular connective tissue connects with that which comes from the periganglionic capsule, forming bands which subdivide the ganglion. The proliferation of the connective tissue of the periganglionic capsule is less marked than is that in the connective tissue around the blood-vessels. The changes in the middle layer of the vessels consist of hyaline and vacuolar degeneration of the muscle-fibers. This occurs principally in the smaller arteries. In two cases we have observed slight perivascular round-cell infiltration.

SUMMARY

From a critical review of previously reported observations, from our observations of control specimens not herein detailed, and from our study of the specimens from the 16 cases herein reported, the following summary presents what we believe to be a fair statement of our present knowledge of the lesions of the cervical sympathetic ganglia in hyperplastic toxic (exophthalmic) goiter:

1. The cells of cervical sympathetic ganglia from patients over forty years of age, and occasionally, though rarely, from those younger, may show hyperchromatization, hyperpigmentation, chromatolysis, and atrophy in minor degrees, commonly designated "cell senility," but due to arteriosclerosis, chronic toxemia, overwork, or other factors which cannot be accurately determined. Of the 16 cases herein studied, only three were over forty years of age. Of these, two (Nos. 4 and 14) showed lesions of the ganglion-cells far beyond those seen in any of our controls. The only case in which the cell-lesions were of such a character and degree as to have permitted their explanation by "senility" was No. 7. In this patient, who was forty-four years of age, the only symptoms of hyperthyroidism were goiter, exophthalmos, Stellwag's, and diarrhea. However, the extreme sclerosis of the ganglion would not appear to be explicable by "senility" alone.

2. Sympathetic ganglia removed more than four hours after death, except under the most favorable mortuary conditions, may show auto-lytic changes, which must be differentiated from pathologic lesions. The ganglia herein studied were all fixed within five minutes after removal from the living patient. Most of our control material from necropsies has been fixed within three hours after death.

3. While van Gieson's stain is valuable for general histologic details, and Nissl's stain for the study of early chromatin changes, the use of Ramón y Cajal's and Levaditi's stains is especially to be recommended for the study of details of late cell destruction. The use of Sudan III in the differentiation of cell-pigment and of Weigert-Luden's stain for myelin is also important.

4. It would appear, from our examination by the methods detailed, that definite histologic changes do occur in the cervical sympathetic ganglia in hyperplastic toxic (exophthalmic) goiter.

5. These histologic changes consist of various stages of degeneration, viz.: (a) Hyperchromatization; (b) hyperpigmentation; (c) chroma-tolysis; and (d) atrophy, or (e) granular degeneration of the nerve-cells. All of these are but successive steps in degeneration, which, if uninter-rupted, proceed to the complete destruction of the ganglion-cells affected. Not all of the ganglion-cells in any of the ganglia examined were so com-pletely destroyed as to render improbable their return to normal under favorable conditions. There is some evidence that in ganglia from cases clinically improved some of the cells have partially or wholly recovered.

6. Some of the ganglia contain cells resembling the partially differ-entiated cells in the ganglia of infants.

7. Accompanying the more advanced changes in the ganglion-cells are similar degenerative changes in the nerve-fibers, and an increase of connective tissue throughout the ganglion, but especially in the outer and middle coats of the vessels and in the perigangionic tissue.

8. So far as may be determined from the small number of observa-tions herein recorded, in the early stages of hyperthyroidism, with ad-vanced parenchymatous hypertrophy and hyperplasia of the thyroid, the total number of cells in the cervical sympathetic ganglia is not greatly reduced, but a very large proportion of the cells present show varying though marked degeneration. The partial remission of clinical symptoms, accompanied by regression of the parenchymatous hypertrophy and hyperplasia in the thyroid, is associated with a much greater reduction in the total number of cells in the ganglia, but of the cells which remain,

relatively fewer show the varying stages of degeneration than in ganglia from patients in the early stages of hyperthyroidism. Thus, in general, the pathologic changes in the cervical sympathetic ganglia are parallel to the stage and intensity of the symptoms of hyperthyroidism, and to the hyperplastic and regressive changes in the thyroid. These statements, however, must be regarded as only tentative, and must await corroboration by carefully correlated clinical and pathologic studies of a much larger number of cases.

9. Whether the changes observed are the result of overstimulation and overwork of the ganglion-cells, as Crile[6] believes is true of the Purkinje cells of the cerebrum, or whether the changes are due to direct toxic action upon the cells themselves, is as yet mere speculation.

REFERENCES

1. Aoyagi, T.: "Studien über die Veränderungen des sympathischen Nervensystems insbesondere der Neurofibrillen bei Morbus Basedowii," Deutsch. Ztschr. f. Nervenh., 1911, xlii, 177–195.
2. Bénard: "Contribution à l'étude du goître exophtalmique," Thèse de Paris, 1882.
3. Berkeley, H. S.: "The Intrinsic Nerves of the Thyroid Gland of the Dog," Johns Hopkins Hosp. Reports, 1895, iv, pt. ii, 113–116.
4. Bonne: Quoted by Chalier, loc. cit.
5. Chalier, A.: "Le traitement de la maladie de Basedow par les opérations dirigées sur le sympathique cervical," Lyon Chir., 1911, v, 172–194; vi, 8–45, 285–304, 555–589.
6. Crile, G. W., and Lower, W. E.: Anoci-association, Phila., Saunders, 1914, 259 p.
7. Crissafulli, E.: "I nervi della glandola tiroide," Bull. mens. della Acad. Gionenia di scienz. nat. in Catania, 1892, n. s., xxv.
8. Dolley, D. H., and Crile, G. W.: "Pathological Cytology of Surgical Shock," Jour. Med. Research, 1909, xx, 275–295.
9. Dolley, D. H.: "Studies on the Recuperation of Nerve-cells After Functional Activity From Youth to Senility," Jour. Med. Research, 1911, xxix, 309–343.
10. Dolley, D. H.: "The Identity in Dog and Man of the Sequence of Changes Produced by Functional Activity in the Purkinje Cells of the Cerebellum," Jour. Med. Research, 1911–12, xxv, 285–311.
11. Eulenberg, A., and Guttmann, P.: "Die Pathologie des Sympathicus; nach den heutigen Erfahrungen dargestellt," Arch. f. Psychiat., 1868–9, i, 420. Quoted by Graupner, loc. cit. (13).
12. Floresco: Quoted by Missiroli, loc. cit. (23).
13. Graupner, R.: "Beiträge zur normalen und pathologischen Anatomie des sympathischen Nervensystems," Beitr. z. path. Anat. u. z. allg. Path., 1898, xxiv, 255–303.
14. Herbet, H.: "Le sympathique cervical," Thèse de Paris, 1900, 256 p.
15. Horand, R.: "Lésions du sympathique cervical dans le goître exophtalmique," Rev. neurol., 1910, xviii, 344. Quoted by Chalier, loc. cit. (5), and abstracted Jour. Nerv. and Ment. Dis., 1911, xxxviii, 303.
16. Horand, R.: "Lésions du sympathique cervical dans le goître exophtalmique; examen histologique de deux nouveaux cas," Rev. neurol., 1911, xix, 669–674.
17. Jaboulay, M.: "De la régénération du goître extirpé dans la maladie de Basedow et la section du sympathique cervical dans cette maladie," Lyon méd., 1896, lxxxi, 389.
18. Jonnesco, T.: "Traitement chirurgical du goître exophtalmique," Cong. franç. de chir., 1896, October 21, p. 320.
19. Kocher, A.: "Ueber Morbus Basedowii," Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1900, ix, 1–304.
20. Levaditi, C.: "Sur la coloration du spirochete pallida Schaudinn dans les coupes," Compt. rend. Soc. de biol., 1905, lix, 326.

21. Luden von Heumen, G.: "Ueber die Anwendung meiner neuen schnellen Weigert-Modification für Paraffinschnitte," Centralbl. f. allg. Path. u. path. Anat., 1912, xxiii, 385–394.
22. Mayo, C. H.: "The Surgical Treatment of Exophthalmos," Jour. Amer. Med. Assoc., 1914, lxiii, 1147–1149.
23. Missiroli, A.: "Sulle alterazioni della ghiandola tiroide in seguito alla resezione del simpatico cervicale," Arch. di fisiol., 1908–9, vi, 582–594, and Path. riv. quidicin. 1908–9, i, 714–716.
24. Möbius, P. J.: "Die Basedow'sche Krankheit," Wien, Hölder, 1896. Forms pt. 2, 22, of Nothnagel's Specielle Pathologie und Therapie, Wien, Hölder, 1894.
25. Neumann, E.: "Das Nervenpigment und die Neuronlehre," Virchow's Arch. f. path. Anat., 1909, cxcvii, 39–44.
26. Ramón y Cajal: Trabajos del lab. de investigaciones biologicas, 1910, viii. Rev. trimestrae micrográfica, xiii.
27. Rhinehart, D. A.: "The Nerves of the Thyroid and Parathyroid Bodies," Amer. Jour. Anat., 1912, xiii, 91–101.
28. Schäfer, E. A.: Text-book of Microscopic Anatomy, London, Longmans, 1912, p. 226. Forms pt. 1, vol. 2, of Quain's Anatomy.
29. Tizzoni, G.: "Sulla patologia sperimentale del gran simpatico," Spallanzani, 1879, viii, 232–242.
30. Trousseau, A.: Cliniques, 1860, v, 571.
31. Vas, F.: "Studien über den Bau des Chromatins in der sympathetischen Ganglienzelle," Arch. für mikros. Anat., 1892, xl, 375–389.
32. Weeks, J. E.: "Pathology of the Cervical Sympathetic," Jour. Amer. Med. Assoc., 1904, xlii, 291–294.
33. White, W. H.: "On the Histology and Function of the Mammalian Superior Cervical Ganglia," Jour. Physiol., 1887, viii, 66–78.
34. White, W. H.: "Further Observation on the Histology and Function of the Mammalian Sympathetic Ganglia," Jour. Physiol., 1889, x, 341–357.
35. Wiener, H.: Quoted by Schäfer, E. "An Introduction to the Study of the Endocrine Glands and Internal Secretions," Stanford Univ. Pub., 1914, p. 33.
36. Wilson, L. B.: "A Method for the Rapid Preparation of Fresh Tissues for the Microscope," Jour. Amer. Med. Assoc., 1905, xlv, 1737.
37. Wilson, L. B.: "Staining Sections of Living Tissue Unfixed," Jour. Lab. and Clin. Med., 1915, i, 40–45.
38. Wilson, L. B.: "The Pathology of the Thyroid Gland in Exophthalmic Goiter," Amer. Jour. Med. Sci., 1913, cxlvi, 781–790, and Tr. Assoc. Amer. Phys., 1913.
39. Wood, F. C.: Quoted by Weeks, loc. cit. (32).

THE PATHOLOGIC CHANGES IN THE SYMPA-
THETIC SYSTEM IN GOITER *

LOUIS B. WILSON

—. ——.

The amount and character of the pathologic changes in the sympathetic ganglia removed at operation or at autopsy from patients with exophthalmic goiter have been studied by other observers, meagerly and rarely by modern methods. I have reviewed elsewhere[1] the literature of previous reports. So far as the findings have been positive they have shown that in exophthalmic goiter the cells of the sympathetic ganglia exhibit various stages of degeneration. The paucity and incompleteness of the reported observations, however, together with Cannon's[2] recent experimental production of some of the symptoms of exophthalmic goiter in cats by constant stimulation of the thyroid through the sympathetic system, have warranted a more careful study of the material accumulating in the Mayo Clinic.

Material for the Present Study.†—The present report is based on a study of the cervical and other sympathetic ganglia removed at autopsy from 12 patients dying during the course of exophthalmic goiter. The observations have been controlled by similar studies on sympathetic ganglia removed at autopsy from 9 patients dying of diseases other than exophthalmic goiter, and by studies on Gasserian ganglia removed at operation from 6 patients with trifacial neuralgia.

All ganglia removed at operation were fixed within five minutes after removal, and the material from autopsies was fixed within three hours after death. Some portions of ganglia were examined in frozen sections of the fresh tissue. The remainder of the specimen or specimens was fixed in 10 per cent. formalin. Selected blocks were cut, frozen without embedding, and the sections stained with Sudan III or by Nissl's method.

footnote* Presented before the Association of American Physicians, Washington, D. C., May 10, 1916. Reprinted from Amer. Jour. Med. Sci., 1916, clii, 799–812.

† For previous report in the present series of observations see: Wilson, L. B., and Durante, L.: "Histologic Changes in the First Sympathetic Ganglion in Exophthalmic Goiter," Jour. Med. Research, 1916, n. s., xxxiv, 273–296.

Other blocks were embedded in paraffin and cut in serial sections, which were stained with hematoxylin-eosin by Weigert-van Gieson's method for connective tissue, by Weigert-Luden's method for myelin,[3] and by Held-Nissl's method for distribution of chromatin. Other blocks were used for silver impregnation by Ramón y Cajal's,[4] Levaditi's,[5] or Biel-schowsky's methods. Others were fixed and stained by Bensley's[6] acetic-osmic-bichromate method for mitochondria. The most satisfactory results were obtained by the use of Sudan III, Held-Nissl's, Ramón y Cajal's, and Bensley's stains.

PROTOCOLS

CASE 1 (A156,845).—The patient was a female, nineteen years of age, who had had severe symptoms of hyperplastic toxic goiter for five months. Recently the thyroid had enlarged very rapidly. The patient died of hyperthyroidism a few days after coming to the Clinic, without having been operated on. At autopsy, three hours and forty minutes after death, there were found marked hyperplasia of the thyroid, marked exophthalmos, symmetric brown pigmentation of the conjunctivæ, marked emaciation, petechial hemorrhages in the skin, in the parietal peritoneum of the true pelvis, and elsewhere in the pelvic organs, marked hypertrophy of the myocardium of the left ventricle, slight nodular sclerosis of the coronary arteries, and fatty changes in the intima. The thymus weighed 80 grams.

Microscopically, the thyroid showed progressive advanced hyper-trophy and hyperplasia, Type B[3]. The superior cervical ganglia showed very marked hyperpigmentation and extensive granular degeneration of the cells, many of which were atrophic or consisted of only small masses of pigment.

CASE 2 (A153,535).—The patient was a female, nineteen years of age; for five months had shown symptoms of severe exophthalmic goiter. Her systolic blood-pressure was 180, diastolic 75, with a pulse-rate of 150 to 168. After two weeks' preparation the left superior thyroid vessels were ligated. Her temperature remained normal and the pulse fluctuated from 100 to 118. Three days after operation she died. The macroscopic findings at autopsy, made three hours and fifteen minutes after death, were those of severe exophthalmic goiter.

Microscopically, the thyroid showed progressive advanced hyper-trophy and hyperplasia, Type B[3]. Many of the cells from the cervical sympathetic ganglia were in the state of advanced degeneration noted in Case 1, though not nearly so many cells were affected (Fig. 272).

CASE 3 (A144,809).—A female, thirty years of age; had had severe symptoms of exophthalmic goiter for eight months. At the time of examination her systolic blood-pressure was 165, diastolic 70, and pulse-

rate 128. The left superior thyroid vessels were ligated, and four months later the right superior thyroid vessels were also ligated. Two weeks after the second ligation the right lobe, isthmus, and pyramidal lobe of the thyroid were extirpated. She died the following day. At autopsy, two hours and thirty minutes after death, an advanced chronic myocarditis with fatty degeneration and advanced degenerative changes in the liver and kidneys were found.

Microscopically, the thyroid showed early regressive advanced hypertrophy and hyperplasia, Type C-1^3. In the cervical sympathetic ganglia a few cells were apparently normal. Many showed varying degrees of hyperpigmentation and granular degeneration (Fig. 273).
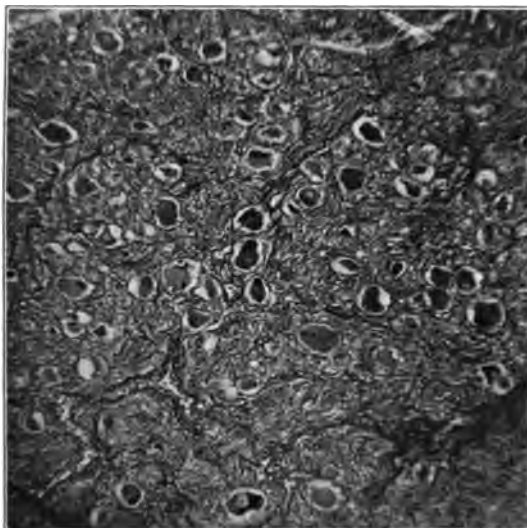
Fig. 272.—(Case 2.) Section of left superior cervical sympathetic ganglion, silver impregnation, 5 microns (× 120 diam.). Advanced degeneration of many cells.

CASE 4 (A136,418).—The patient, a female twenty-five years of age, had shown symptoms of exophthalmic goiter for two years, with marked increase in severity during the last three weeks. At the time of examination her systolic blood-pressure was 145, and diastolic 80. The left superior thyroid vessels were ligated, and five days later the right superior vessels were ligated also. Four and a half months later the right lobe, isthmus, and a small portion of the left lobe of the thyroid were resected. The patient died nine days after the operation. At autopsy, eight hours after death, the macroscopic findings were a hypertrophied thymus, acute myocardial degeneration, and dilatation of the heart, congestion and degeneration of all parenchymatous organs, and severe purulent bronchitis. The cervical sympathetic ganglia were noticeably enlarged.

'16—37

Microscopically, the thyroid showed early regressive advanced parenchymatous hypertrophy and hyperplasia, Type C–1³. The ganglia showed
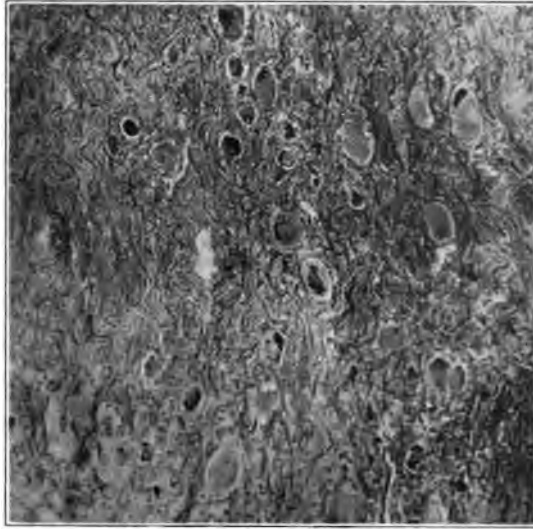
Fig. 273.—(Case 3.) Section of left superior cervical sympathetic ganglion, silver impregnation, 5 microns (× 120 diam.). A few normal cells, many showing advanced degeneration.
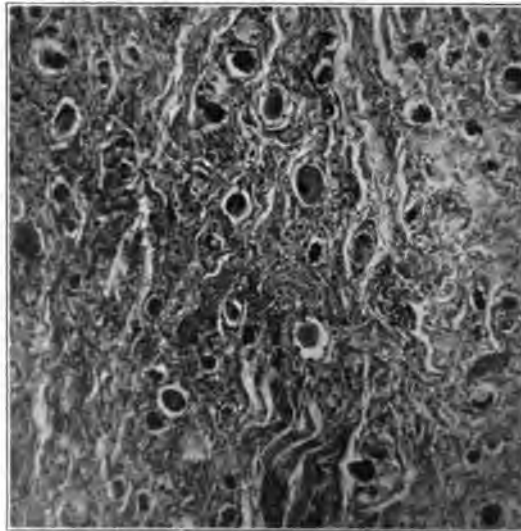
Fig 274.—(Case 4.) Section of right superior cervical sympathetic ganglion, silver impregnation, 10 microns (× 120 diam.). A few normal cells, many in varying stages of degeneration.

a few fairly normal cells, but many others in varying stages of degeneration (Fig. 274).

CASE 5 (A11,264).—This patient was a female thirty-three years of age, who had had symptoms of exophthalmic goiter beginning two years and five months previously. At the time of examination her systolic blood-pressure was 138, diastolic 90, and pulse-rate 138. The left superior thyroid vessels were ligated, and two weeks later the right superior thyroid vessels. Two and three months after the last ligation hot-water injections were made into each lobe of the thyroid, and three weeks after this, or four and a half months after the first ligation, the right lobe and isthmus of the thyroid were extirpated. The patient's pulse-rate increased to 140, and she died twenty-four hours after the operation. At autopsy, two hours and thirty minutes after death, the principal macroscopic findings were acute and chronic myocardial degeneration, with a dilated heart, general parenchymatous degeneration not so severe as usual in exophthalmic goiter, and chronic nephritis.

Microscopically, the thyroid showed early regressive advanced hypertrophy and hyperplasia, Type C–1^3. A few cells in the cervical sympathetic ganglia were normal. Many showed varying degrees of hyperpigmentation and granular degeneration.

CASE 6 (A149,095).—The patient, a female twenty-eight years of age, had shown symptoms of exophthalmic goiter for six years, with a maximum severity within the first year. At the time of examination she had slight exophthalmos, a systolic blood-pressure of 150, a diastolic of 80, and a pulse-rate of 120. The left superior thyroid vessels were ligated, and two weeks later hot-water injections were made into the right lobe of the thyroid. One week after this the right superior thyroid vessels were divided and the ends ligated separately. Two weeks after the last operation the patient died. At autopsy, one hour after death, the principal macroscopic findings were bilateral lobar pneumonia with infarction of right upper lobe and hypertrophy and dilatation of the heart.

Microscopically, the thyroid showed a regressing advanced hypertrophy and hyperplasia, Type C–2^3. The cervical sympathetic ganglia showed many cells apparently normal, a few in advanced stages of degeneration, and a very few in intermediate stages of degeneration.

CASE 7 (A135,172).—The patient, a female twenty-nine years of age, had had goiter for sixteen years, with moderate symptoms of thyrotoxicosis for twelve years, the maximum severity of toxic symptoms having been attained about four years ago, since which time there had been some abatement. At the time of examination the systolic blood-pressure was 175, the diastolic 78, and the pulse-rate 114. The left and right superior thyroid vessels were ligated, and four months later the right lobe, isthmus, and a small piece of the left lobe of the thyroid were extirpated. The patient died one week after operation. At autopsy, two hours after death, the macroscopic findings were a hypertrophied thymus, bilateral emphysema, acute splenitis, and chronic nephritis with congestion.

Microscopically, the thyroid showed advanced regressive changes on

chronic hypertrophy and hyperplasia, Type C–2³. The superior cervical sympathetic ganglia showed many cells apparently normal and a few in advanced stages of degeneration. The total number of cells was apparently much reduced (Fig. 275).

CASE 8 (A109,170).—This patient, a female forty-seven years of age, had noticed enlargement of the thyroid for four years, but with symptoms ascribable to thyrotoxicosis, beginning only one year prior to the enlargement. At the time of examination her systolic blood-pressure was 140, diastolic 45, and pulse-rate 120. The right and left superior thyroid vessels were ligated. She improved steadily in health for eight or nine months, and then began to lose appetite, weight, and strength. A year after the first operation several hot-water injections into the thyroid were
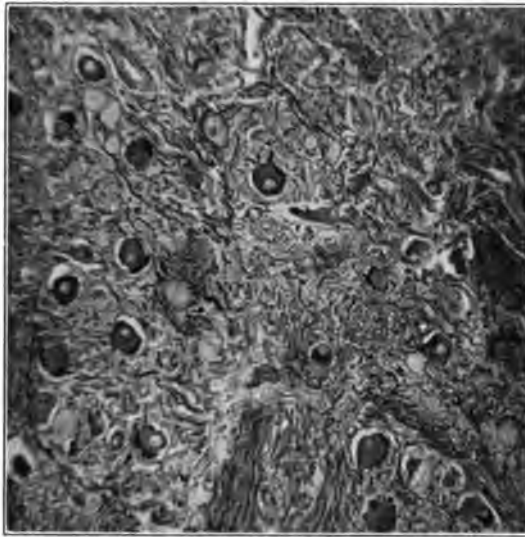
Fig. 275.—(Case 7.) Section of right superior cervical sympathetic ganglion, silver impregnation, 5 microns (× 120 diam.). Marked reduction in the number of cells, many apparently normal, and a few in advanced stages of degeneration.

made. The patient's general health improved, but her blood-pressure rose to 166 systolic, 90 diastolic, and pulse-rate to 140, six months after the injections. One month later her pulse-rate had risen to 176. A month after this, or one year and eight months after the first operation, she died. At autopsy, three hours after death, the macroscopic findings were hypertrophy and dilatation of the heart, chronic cholecystitis, and parenchymatous degeneration of all organs.

Microscopically, the thyroid showed advanced regression on an old parenchymatous hypertrophy and hyperplasia, Type C–3³. The superior cervical sympathetic ganglia showed a great reduction in the total number of cells, many of the remaining ones of which, however, were normal, while a few were in advanced stages of granular degeneration.

CASE 9 (A147,479).—The patient, a female forty-four years of age, had had thyroid enlargement for thirty-two years, with symptoms of thyrotoxicosis, beginning five years ago and gradually increasing to the present time. At the time of examination the patient had lost weight from 150 to 114 pounds. Her systolic blood-pressure was 122, diastolic 80, and her pulse-rate was 120. She died without operation. At autopsy, two hours and forty-five minutes after death, the macroscopic findings were a medium-sized retrotracheal thyroid, hemopericardium and right hemothorax with adhesions, and acute parenchymatous degeneration with fatty changes in the heart, liver, kidneys, and chronic nephritis.

Microscopically, the thyroid showed advanced regression on chronic parenchymatous hypertrophy and hyperplasia, Type C–3³. The superior
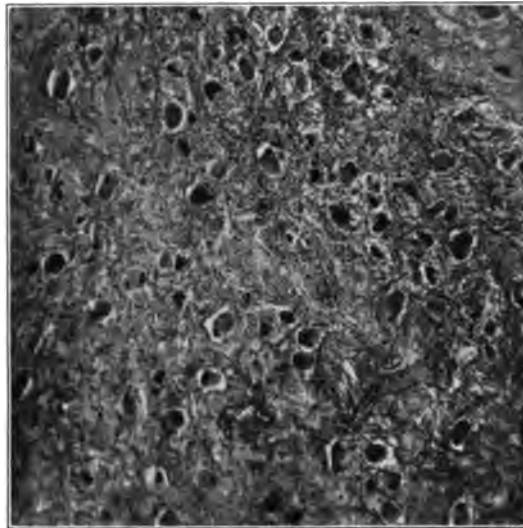
Fig. 276.—(Case 9.) Section of right superior cervical sympathetic ganglion, silver impregnation, 10 microns (× 120 diam.). Many normal cells, many hyperpigmented, and a few in advanced stages of degeneration.

cervical sympathetic ganglia showed a marked reduction in the total number of cells present. Of those present, many were normal, and a few were in advanced stages of degeneration (Fig. 276).

CASE 10 (A67,759).—The patient, a female fifty years of age, had had enlargement of the thyroid for twenty years, with mild symptoms of thyrotoxicosis beginning coincident with the thyroid enlargement and lasting for three years. Six months previous to examination the symptoms of thyrotoxicosis returned. At the time of examination the patient was emaciated, the pulse-rate was 200, with a cardiac arrhythmia growing progressively worse. She died three days after examination. At autopsy, one hour after death, the principal macroscopic findings were enlarged thyroid, myocarditis, atrophic and fatty changes in the liver, and chronic nephritis.

Microscopically, the thyroid showed advanced regressive changes in parenchymatous hypertrophy and hyperplasia with some adenomatosis, Type C-3³. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Most of those present, however, were fairly normal, while a few showed advanced degenerative changes.

CASE 11 (A156,404).—The patient, a female fifty-five years of age, had had thyroid enlargement for twenty-four years. A thyroidectomy of the right lobe was done six years before, followed by a remission of all symptoms until a recent onset of cardiac distress. At the time of examination she had lost weight from 150 to 135 pounds; had a systolic blood-pressure of 158, and a diastolic of 88. The left lobe of the thyroid was extirpated and the internal jugular on the left side ligated. The patient
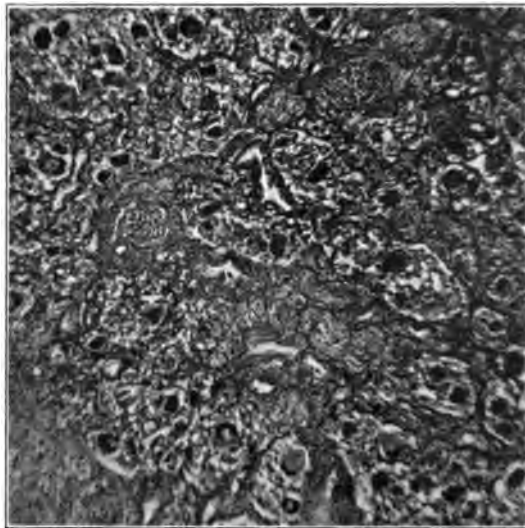
Fig. 277.—(Case 11.) Section of left superior cervical sympathetic ganglion, silver impregnation. 10 microns (× 120 diam.). Marked reduction in the number of cells, many normal, and many in varying stages of advanced degeneration; marked increase of fibrous connective-tissue.

died three days after operation. At autopsy, two hours and thirty minutes after death, the macroscopic findings were marked acute edema of the glottis, moderate hypertrophy of the myocardium of the left ventricle, marked disseminated nodular thickening of the aorta and of the aortic and mitral valve leaflets, and a moderate sclerosis of the coronary arteries.

Microscopically, the thyroid showed advanced regression of a moderate hypertrophy and hyperplasia, with considerable adenomatosis, Type C-3³. The superior cervical sympathetic ganglia showed a marked reduction in the total number of cells. Of the cells present, many were normal, but a large number were in varying stages of advanced regeneration. There was marked increase of fibrous connective-tissue in the ganglia (Fig. 277).

SUMMARY OF PROTOCOLS.—A study of the preceding protocols shows that of the 11 patients, 7 were females between nineteen and thirty-nine years of age and 4 were females between forty-eight and fifty-five years of age.

When considered in relation to the duration and stage of the symptoms of exophthalmic goiter, the cases may be roughly grouped into three classes:

A. Cases still presenting active progressive symptoms of hyperplastic toxic (exophthalmic) goiter. These are as follows:

  1. (A156,845) Female, aged nineteen years, symptoms five months, severity 3.*
  2. (A153,535) Female, aged nineteen years, symptoms five months, severity 2 to 3.
  3. (A136,418) Female, aged twenty-five years, symptoms two years, severity 3.
  4. (A144,809) Female, aged thirty years, symptoms eight months, severity 3.

B. Cases in which the severity of the symptoms of hyperplastic toxic goiter had partially subsided, though the acute toxic condition was yet present. These are as follows:

  5. (A11,264) Female, aged thirty-three years, symptoms two years, present severity 2.
  6. (A149,095) Female, aged twenty-eight years, symptoms six years, severity 3.

C. Cases in which the acute toxic symptoms had almost, if not completely, subsided. These are as follows:

  7. (A135,172) Female, aged thirty-nine years, goiter for sixteen years, maximum severity four years ago 3, present severity 1.
  8. (A109,170) Female, aged forty-eight years, goiter four years, symptoms five years, present severity 1.
  9. (A147,479) Female, aged forty-nine years, goiter thirty-two years, symptoms for two years, present severity 1 to 2.
  10. (A67,759) Female, aged fifty years, goiter for twenty years, symptoms during first three years of goiter, then remission until during last six months, present severity 1.
  11. (A156,404) Female, aged fifty-five years, goiter twenty-four years, thyroidectomy right lobe six years ago for doubtful exophthalmic goiter, remission until recent onset of cardiac distress.

The first 4 cases may be grouped with 5 others previously reported[1] in which only the ganglia removed at operation were examined. In

*On a scale of 1 to 5, in which 5 represents the greatest severity.

these 9 cases of acute progressive hyperplastic toxic goiter there was very marked hyperpigmentation with extensive granular degeneration, and in some cases atrophy of the ganglion-cells.

Cases 5 and 6 may be grouped with three operative cases previously reported.[1] These 5 cases showed considerable hyperpigmentation and granular degeneration, though a smaller number of cells were involved than in the ganglia from the cases of the first group.

Cases 7, 8, 9, 10, and 11 may be grouped with 6 other previously reported[1] operative cases. These 11 cases all showed a very marked regression or complete absence of toxic symptoms at the time of operation or death. In the ganglia from all these the hyperpigmentation and granular degeneration affected a relatively small percentage of the cells present. In many of the cases, however, a marked diminution in the total number of cells present in the ganglion was shown by sections in series including the entire ganglion.

DISCUSSION.—Thus it will be seen that roughly the degree of hyperpigmentation, the amount of granular degeneration, the atrophy and the reduction in the number of cells were in direct relation to the continuation and subsequent remission of the symptoms of hyperthyroidism. Parallel with this, the perivascular connective tissue and the connective-tissue stroma generally throughout the gland were increased in direct ratio to the time during which the symptoms of hyperthyroidism had continued. In two of the cases there was marked sclerosis of the ganglionic connective tissue.

Though the present number of cases is too small from which to draw positive conclusions, the observations so far seem to indicate that early in acute hyperplastic toxic goiter there is present in the superior cervical, and probably also in some degree in the other sympathetic ganglia, a process which is causing active stimulation, overfunction, and progressive stages of degeneration in the ganglionic cells. As the symptoms of exophthalmic goiter regress, evidence is found in the ganglia of the cessation of this degenerative process in the ganglionic cells not previously changed past recovery. After the acute toxic symptoms have entirely ceased for years there remains little evidence of the destroyed ganglionic cells, most of the fatty pigmentary remains of the cells apparently having been absorbed.

The problems of the pathologic changes in the sympathetic ganglia in man have been obscured in the past by the occasional presence of pigment in the ganglion-cells from patients who had exhibited no symptoms of involvement of the sympathetic system. Normally, the cells of

the sympathetic ganglia in man are relatively free from pigment until adult life. They then may acquire more or less extensive deposits of brown pigment-granules, arranged crescentically about 'the nuclei. The ganglion-cells of patients dying of prolonged wasting diseases, such as tuberculosis and cancer, are apt to show an increased amount of pigmentation and in some instances varying stages of degeneration, hyperchromatization, chromatolysis, and granular degeneration. As control material in these respects many ganglia have been studied by methods parallel to those used on the ganglia from the goiter cases.

CONTROLS.—The control autopsy material is as follows:

1. (A139,228) Eight months' fetus. Placenta prævia; atelectasis. Ganglionic cells normal; no pigmentation.

2. (A138,548) Eight months' infant. Pneumonia, following operation for harelip. Ganglionic cells normal; no pigmentation.

3. (A149,999) Female, aged seventeen years. Pituitary tumor. Death following puncture of corpus callosum. Dilatation of heart; acute nephritis; fatty liver. The lymph-spaces around the ganglionic cells are much dilated; the cells are shrunken and hyperchromatic, but not pigmented nor degenerated.

4. (A139,228) Female, aged thirty-six years. Placenta prævia; mother of fetus Case 1. Normal; no pigmentation nor degeneration of the cells of the cervical ganglia.

5. (P. B. H. No. 61) Male, aged thirty-four years. Acromegaly; colloid goiter. No pigmentation and no degeneration in ganglia found.

6. (A149,288) Male, aged thirty-five years. Congenital cystic kidneys; hematuria. Some pigmentation, but no degeneration of the ganglionic cells.

7. (38 P. B. H. 3289) Male, aged thirty-eight years. Acromegaly. Some hyperchromatolysis and hyperpigmentation; no granular degeneration of cells found.

8. (A136,199) Male, aged fifty-two years. Carcinoma of anterior wall of stomach; acute parenchymatous nephritis. Autopsy five hours after death. Considerable pigmentation of ganglion-cells; no degeneration.

9. (A134,342) Male, aged sixty-four years. Carcinoma of stomach; coronary sclerosis; myocarditis; chronic nephritis. Pericellular lymph-spaces of ganglia dilated; cells shrunken; feeble staining; little pigmentation; no degeneration.

The operative control material consists of Gasserian ganglia removed

from six patients with trifacial neuralgia in the Mayo Clinic, and from one patient in the Peter Bent Brigham Hospital, and one cervical sympathetic ganglion removed in the Mayo Clinic because of its apparent involvement in a male patient fifty years of age in whom the primary lesion had been a persistent branchial cyst. Although the Gasserian ganglia in the 6 cases of trifacial neuralgia and the cervical sympathetic in the branchial cyst case were all the subject of ganglionic or periganglionic chronic inflammatory changes, and although the patients were from forty-one to seventy-one years of age, in none of the ganglia was there found evidence of such extensive degeneration of the ganglion-cells as in the cases of exophthalmic goiter. In all the cases there was more or less increase of pigment over that found in the ganglia of young adults, but in no case was the amount comparable with that found in exophthalmic goiter cases. Destruction of the ganglionic cells was apparently absent.

Thus it is suggested that neither advanced age, chronic wasting disease, nor chronic inflammatory processes necessarily cause degenerative changes in the sympathetic ganglia resembling those in exophthalmic goiter.

INVOLVEMENT OF OTHER GANGLIA.—The question is suggested whether the involvement of the superior and middle cervical sympathetic ganglia in exophthalmic goiter is but a part of a general metabolic disturbance evidenced by similar changes in the sympathetic ganglia elsewhere in the body, or whether it is confined to the cervical sympathetic ganglia alone. In only 4 cases in which the cervical sympathetic ganglia were shown to be involved have we been able to study the ganglia from other portions of the body. In none of these was there positive evidence of involvement other than hyperpigmentation. There was little or no granular degeneration present resembling that found in the middle and superior cervical sympathetic ganglia. These observations will, of course, need to be confirmed by a much larger series of cases, but they suggest that the ganglionic changes in exophthalmic goiter may be confined largely to the cervical sympathetics, and that they may not be a secondary result of a general metabolic disturbance.

EXPERIMENTAL WORK.—With a view to determining the possible relationship of the lesions in the sympathetic ganglia to exophthalmic goiter, studies have been made of the ganglia in a number of animals (dogs, goats, spermophiles, rabbits, and monkeys), in some of which many of the symptoms of exophthalmic goiter had been produced by

the administration of Kendall's alpha-iodin, in others which had been subjected previously to double thyroidectomy, and in others in which the cervical ganglia had been injected with various bacteria. In only one animal, however, were suggestive degenerative changes found in the ganglionic cells. In this animal, a young male goat, a small amount of a virulent broth culture of Bacillus bronchisepticus (the bacillus associated with canine distemper and an organism which frequently affects the central nervous system) was injected into the right superior cervical ganglion. The animal died twenty-four days later, and necropsy was performed within an hour after death. The superior cervical sympathetic ganglion from the left side and the stellates from both sides were all apparently normal. The right superior cervical sympathetic, which had received the injection, showed at the immediate site of the injection a small area in which the ganglionic cells were completely destroyed and replaced by necrotic tissue. Throughout the remainder of the ganglion the cells were highly pigmented and showed various degrees of advanced degeneration. In fact, the lesions were quite parallel with those in the cervical ganglia removed from patients with acute exophthalmic goiter.

These experiments are being repeated, and will be made the subject of a subsequent report.

In conclusion, I wish to thank Professors William T. Councilman, Harvey Cushing, and Walter B. Cannon, of the Harvard Medical School, for kindly permitting me to examine their ganglionic material from autopsies, operations, and animal experiments.

REFERENCES

1. Wilson, L. B., and Durante, L.: "Histologic Changes in the First Sympathetic Ganglion in Exophthalmic Goiter," Jour. Med. Research, 1916, n. s., xxxiv, 273–296.
2. Cannon, W. B., Binger, C. A. L., and Fritz, R.: "Experimental Hyperthyroidism," Amer. Jour. Physiol., 1914–15, xxxvi, 363–364.
3. Luden (von Heumen), G.: "Ueber die Anwendung meiner neuen schnellen Weigert-Modification für Paraffinschnitte," Centralbl. f. allg. Path. u. path. Anat., 1912, xxiii, 385.
4. Ramón y Cajal: Trabajos des Lab. de Investigaciones Biologicas, 1910, viii. Rev. trimestral micrografica, xiii.
5. Levaditi, C.: "Sur la coloration du spirochæta pallida Schaudinn dans les coupes," Compt. rend. Soc. de biol., 1915, lix, 326.
6. Bensley, R. R.: "Studies on the Pancreas of the Guinea-pig," Amer. Jour. Anat., 1911–12, xii, 308.
7. Wilson, L. B.: "The Pathology of the Thyroid Gland in Exophthalmic Goiter," Amer. Jour. Med. Sci., 1913, cxlvi, 731, and Tr. Assn. Amer. Phys., 1913.
8. Kendall, E. C.: "Isolation in Crystalline Form of the Compound Containing Iodin, which Occurs in the Thyroid," Jour. Amer. Med. Assoc., 1915, lxiv, 2042, and Tr. Assn. Amer. Phys., 1915, xxx, 420.

FURTHER STUDY OF THE HISTOPATHOLOGY OF THE AUTONOMIC NERVOUS SYSTEM IN GOITER *

LOUIS B. WILSON

WITH A NOTE ON THE SPECIAL TECHNIC OF RECONSTRUCTIONS AT HIGH MAGNIFICATIONS

THOMAS O. YOUNG

Many of the older clinical writers classified exophthalmic goiter as a disease of the sympathetic nervous system. It is only in recent years that the primary importance of the thyroid has become recognized. Although we must give full weight to overfunction of the thyroid as the direct cause of hypermetabolism, which is the dominant factor in the syndrome designated "exophthalmic goiter," it must be confessed that when we attempt to explain the primary cause of overfunction of the thyroid all our hypotheses are unsatisfactory.

Cannon[1] has shown that by constant stimulation of the thyroid produced by anastomosing the phrenic nerve with fibers of the cervical sympathetic he has been able to produce many of the symptoms of hyperthyroidism. McCarrison[2] has adduced a large mass of data, both clinical and experimental, supporting the hypothesis that both simple and exophthalmic goiter are due to water-borne infection. However, the theory that the thyroid is excited beyond its normal function by infection within the gland has received little supporting evidence in the bacteriologic findings, in the histologic appearance of local inflammation, or in the clinical course of the disease.

Some time ago, in an examination of the changes in the various skeletal muscles in cases of exophthalmic goiter, I was struck by the extremely erratic distribution of the degeneration in the various muscle-fibers and

bands. Such an erratic distribution is difficult to explain on any theory of work-change or of the irregular vascular distribution of a blood-borne toxin. On the other hand, it might readily arise from the irregular destruction of selected neurons, or portions thereof, controlling the various muscle-bundles. In consideration of these facts from the clinical, experimental, bacteriologic, and histologic standpoints I was led to investigate more carefully the histopathology of the autonomic nervous system in relation to goiter.

Previous Reports in the Present Series of Observations

Durante and I[3] have recently reported our observations on 20 superior cervical sympathetic ganglia removed at operation from 16 patients with hyperplastic toxic (exophthalmic) goiter. Our findings may be briefly summarized as follows:

1. Definite histologic changes in the cells of the cervical sympathetic ganglia in hyperplastic toxic (exophthalmic) goiter occurred in all cases examined.

2. These histologic changes consisted of various stages of degeneration, namely: (a) hyperchromatization; (b) hyperpigmentation; (c) chromatolysis; and (d) atrophy or (e) granular degeneration of the nerve-cells.

3. Some of the ganglia contained cells resembling the partially differentiated cells found in the ganglia of infants.

4. Accompanying the more advanced changes in the ganglion-cells were similar degenerative changes in the nerve-fibers and an increase of connective tissue throughout the ganglion, but especially in the outer and middle coats of the vessels and in the periganglionic tissue.

5. So far as could be determined from the small number of observations, the pathologic changes in the cervical sympathetic ganglia were parallel to the stage and intensity of the symptoms of hyperthyroidism and to the hyperplastic and regressive changes in the thyroid.

In addition to the above, I have recently reported[4] my observations on a study of the cervical sympathetic ganglia removed at autopsy from 12 patients dying during the course of exophthalmic goiter, the observations on which were controlled by similar studies on sympathetic ganglia removed at autopsy from patients dying of diseases other than exophthalmic goiter and by studies of Gasserian ganglia removed at operation from patients with trifacial neuralgia. The results of these latter studies show that the changes in the ganglia cases of exophthalmic goiter coming

to autopsy are parallel in all respects with those in the ganglia removed
at operation, while the ganglia removed from patients coming to autopsy
from other diseases and the ganglia removed at operation for conditions
other than exophthalmic goiter furnish valuable negative controls. In
the latter report I have also included a brief preliminary note of experi-
mental work in the production of the degenerative changes in the gan-
glionic cells. In one animal (goat) lesions parallel wtih those in the cer-
vical ganglia removed from patients with acute exophthalmic goiter were
produced by the injection into the capsule of the ganglion of a virulent
culture of Bacillus bronchisepticus, the bacillus associated with canine
distemper. This experimental work is still in progress, and will be made
the subject of a subsequent report.

SUBJECT MATTER OF PRESENT STUDY

I wish to present more in detail and from a different viewpoint the
general character of the histologic lesions. The study of these turns on
the irregularity of their distribution, their extent, and the probable order
of the various phases of degeneration.

When one studies the pathologic changes in isolated sections of the
ganglia, it is difficult to determine the exact distribution of affected cells,
though even in studying non-serial sections he is struck by the presence
of apparently perfectly normal cells in immediate opposition to others
that appear to be in advanced stages of degeneration. Since, however.
the ganglion-cells are of much greater diameter than the thickness of
good paraffin sections, it is possible to interpret the apparent irregulari-
ties in size and irregular distribution of pigment in the ganglionic cells
in a single section on the theory that they are the result of oblique cuts
including only small portions of cells. In order, therefore, to determine
the extent of the destruction of the cells one must study series of sections
at least of sufficient extent to include all portions of a group of ganglionic
cells selected in a given microscopic field in a section near the middle of
the series. All preceding and succeeding sections in which these indi-
vidual cells appear must be studied. I recognized this principle early in
the work, and all material has been studied in such serial preparations.
One is able thus to demonstrate beyond a doubt the character and extent
of the changes in a given group of ganglion-cells.

This summer Mr. T. O. Young, a medical student in the University
of Minnesota, under my direction has prepared a number of Born wax

reconstructions of groups of cells selected as above indicated. A description of his technic is herewith appended.

All the reconstructions were made at a magnification of 600 diameters, photographed down to a magnification of 300 diameters, and are herewith reproduced at a magnification of 200 diameters. In examining them the fact must not be lost sight of that they represent groups of cells selected as above indicated; *i. e.*, those of each of which some portion appears in a single section of the series. Thus while all portions of each cell in the group are shown, the group itself covers the distribution of
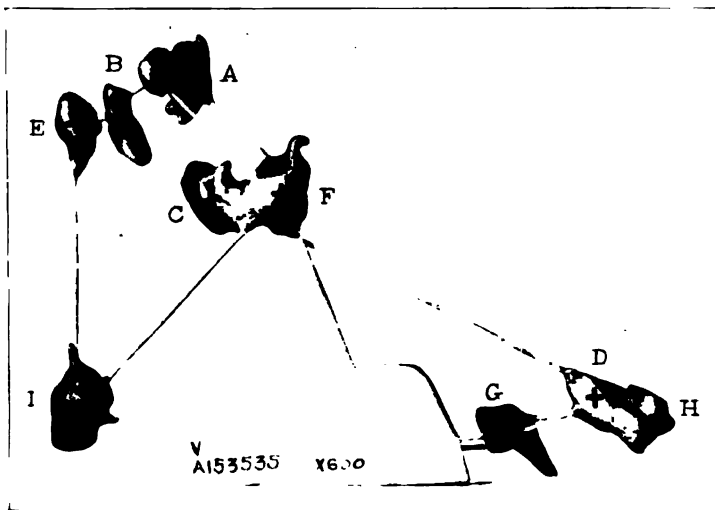
Fig. 278.

the cells in two dimensions only. The interior details of the cells can, of course, be represented in the opaque models only diagrammatically and by arbitrary signs. With these, however, and the knowledge that the relative shape and size of the cells have been preserved, the analysis is interesting.

PROTOCOLS

CASE 1 (A153,535, Fig. 278). (For previously reported details of this case see Case 2 in article Ref. 4.)   This reconstruction is from a group of ganglion-cells in the left superior cervical sympathetic ganglion of a female nineteen years of age who had had severe symptoms of exophthalmic goiter for five months. Of the nine cells shown, four, A, B, C, and D, are apparently normal, and five, E, F, G, H, and I, are pigmented.
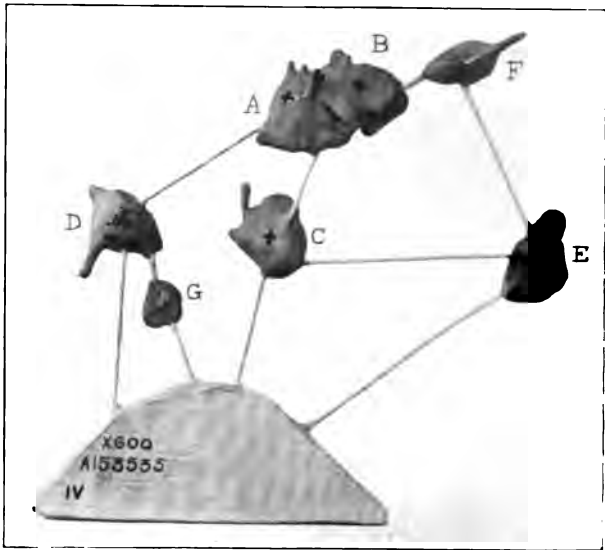
Fig. 279.
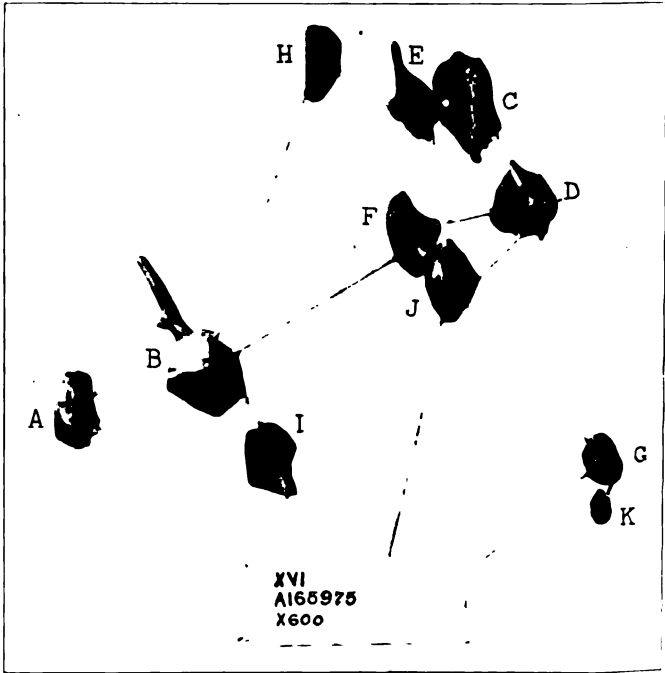
Fig. 280.

In one, I, the most pigmented, the nucleus has disappeared; in the other eight the nuclei show no changes of sufficient importance to warrant our designating them as degenerated.

Fig. 279: This reconstruction is from another area in the same ganglion as that shown in Fig. 278. In this area three cells, A, B, and C, are apparently normal, and four, D, E, F, and G, are pigmented. In two,
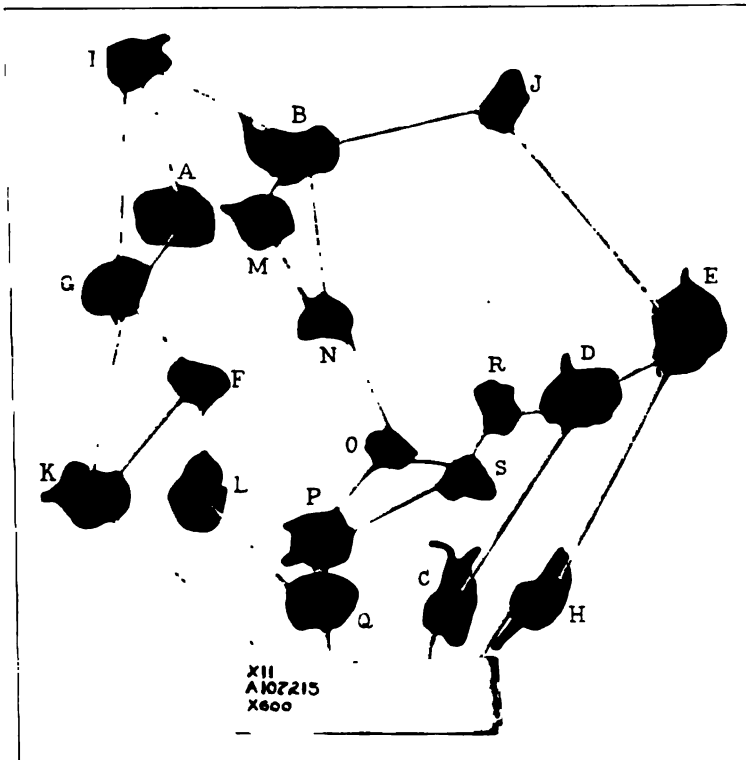
Fig. 281.

D and E, the nuclei are in an advanced stage of degeneration; in the other two, F and G, they have completely disappeared.

CASE 2.—(A165,975, Fig. 280.) This reconstruction is from a group of ganglion-cells in the right superior cervical sympathetic ganglion of a male thirty years of age who had had severe symptoms of exophthalmic goiter for three months. His left superior thyroid vessels had been ligated nine days, and his right superior thyroid vessels four days, before his death, the immediate cause of which was a bilateral disseminated bronchopneumonia. His myocardium showed very marked fatty

'16—38

changes. Of the 11 cells shown, four, A, B, C, and D, are apparently normal, both in their cytoplasm and nuclei. One, E, is atrophied and the nucleus is in an advanced stage of degeneration, but without pigmentation in the cytoplasm. In two, F and G, there are advanced destruction of the nuclei, atrophy, and advanced pigmentation. In two, H and I, there are atrophy and complete destruction of the nuclei, but no pigmentation. In one, J, there are some atrophy, advanced pigmentation,
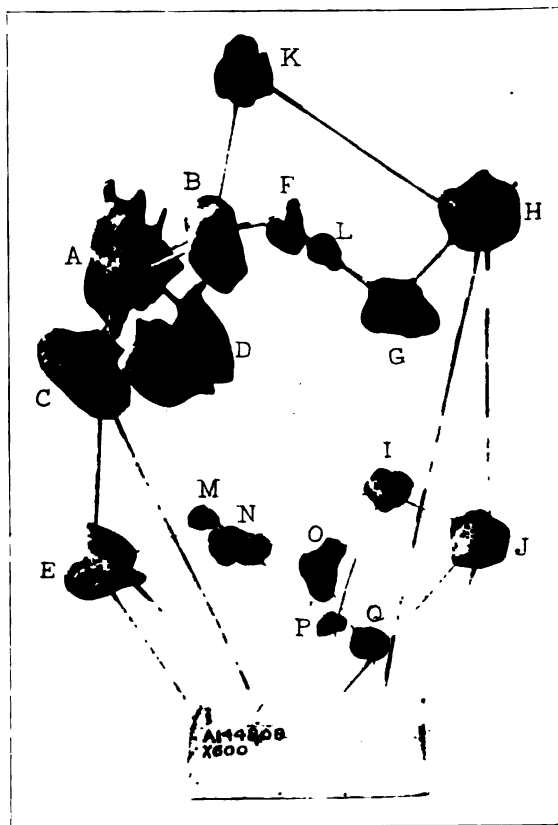
Fig. 282.

and complete destruction of the nucleus. Of one, K, only a mass of pigment about one-eighth the normal size of the cell remains.

CASE 3.—(A107,215, Fig. 281. Case 1, Ref. 3.) This reconstruction is from a group of ganglion-cells in the left superior cervical sympathetic ganglion of a female twenty-four years of age who had had symptoms of severe exophthalmic goiter for four months. Of the 19 cells shown, five, A, B, C, D, and E, are apparently normal in size.

character of protoplasm, and the nuclei. One other, F, may be normal, although it is quite small. Two, G and H, are heavily pigmented but show nuclei which are apparently normal. Four, I, J, K, and L, are heavily pigmented and show no nuclei. Five, M, N, O, P, and Q, are atrophic, show no pigment, but are without nuclei. Two, R and S, are reduced to relatively small masses of pigment only.

CASE 4.—(A144,809, Fig. 282. Case 3, Ref. 4.) This reconstruction is from a group of ganglion-cells of the left superior cervical sympathetic ganglion of a female thirty years of age who had had severe exophthalmic goiter for eight months. Of the 17 cells shown, two, A and B, show apparently normal protoplasm and nuclei, though they
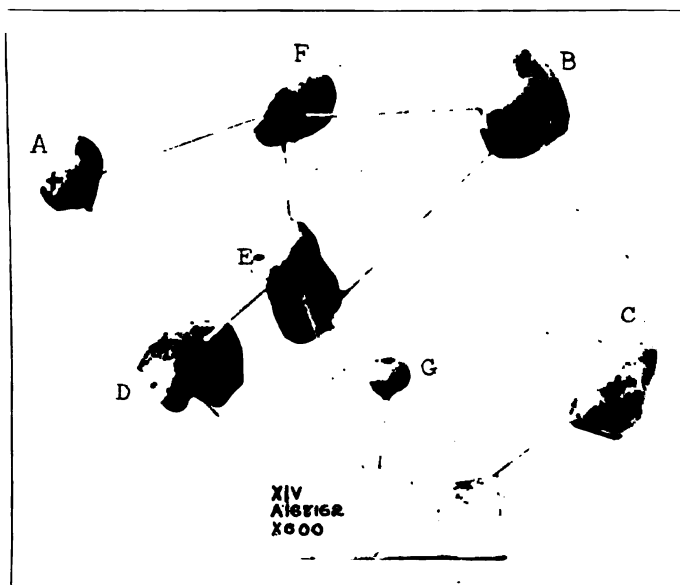
Fig. 283.

are hypertrophied. One other, C, near them is markedly hypertrophied, and though its nucleus is normal it shows beginning pigmentation. Another, D, in the immediate vicinity, is markedly hypertrophied, shows beginning pigmentation, and its nucleus has completely disappeared. One, E, which is normal in size, shows beginning degeneration of the nucleus and no pigmentation. Three others, F, G, and H, though showing no pigmentation, show complete destruction of the nucleus. Two, I and J, show advanced pigmentation with destruction of the nucleus, and seven, K, L, M, N, O, P, and Q, are reduced to atrophic masses of solid pigment.

CASE 5.—(A167,162, Fig. 283.) This reconstruction is from a group

of ganglion-cells in the right superior cervical sympathetic ganglion of a female twenty-four years of age who had had very severe symptoms of exophthalmic goiter for three months, remission of symptoms for four months, a severe relapse for two months, and then almost complete remission of all symptoms except severe exophthalmos during the last six months preceding operation (sympathectomy). Throughout the sections from this case hypertrophy of the ganglion-cells was marked. In the group shown one cell, A, is apparently normal in size, composition
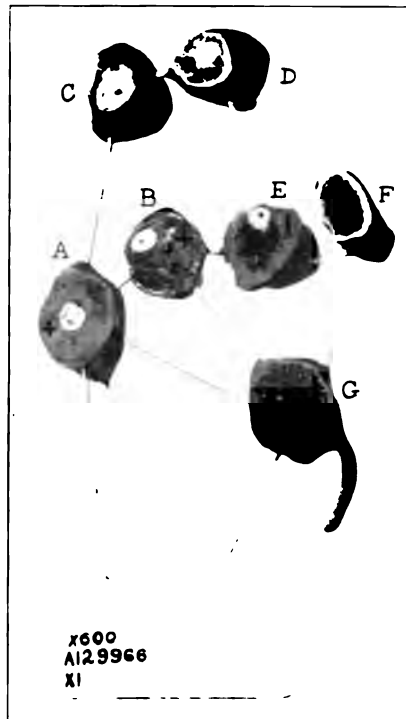
Fig. 284.

of its protoplasm, and character of its nucleus. Two, B and C, are very markedly hypertrophied, but with nuclei which show no degenerative changes. One, D, is hypertrophied and pigmented, but with an apparently normal nucleus. Another, E, is hypertrophied, with an apparently normal nucleus. Another, F, is pigmented and shows no nucleus. Another, G, is atrophied, non-pigmented, and without a nucleus.

CASE 6.—(A129,966, Fig. 284. Case 2, Ref. 3.) This reconstruction is from a group of ganglion-cells in the left superior cervical sympathetic ganglion of a female thirty years of age who had had severe

symptoms of exophthalmic goiter for a year.   An examination of the sections from this ganglion showed in most areas a marked atrophy of the ganglion-cells.   The group selected for reconstruction is from an area in which the cells are hypertrophied.   In the model each cell is bisected, and on the cut surface are indicated the pigmentation and appearance of nuclei; the latter is also indicated by the arbitrary signs. A photograph has been taken of the model with the loose portion of each cell removed.   Of the seven cells shown, none are normal, though two,
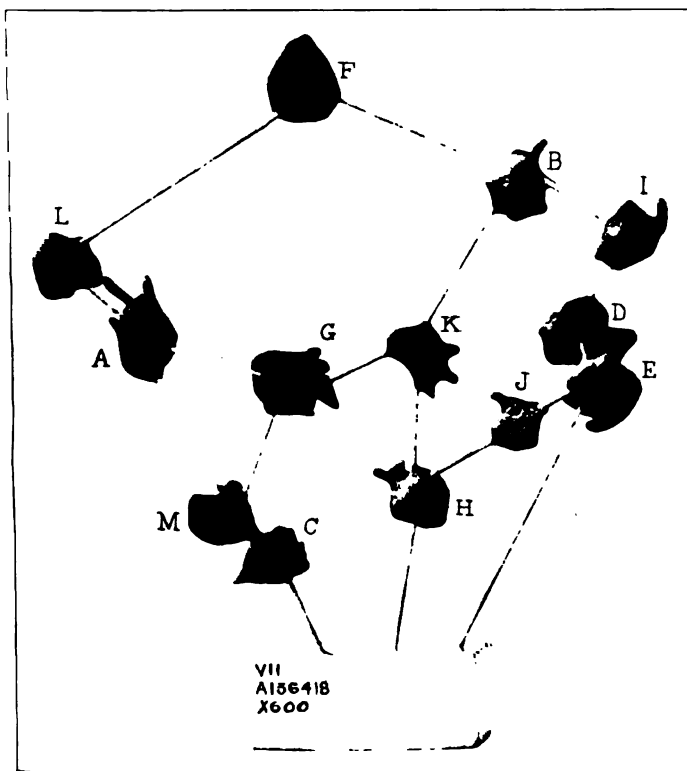
Fig. 285.

A and B, show nuclei without material degeneration; in three others, C, D, and E, degeneration has begun in the nuclei, and in two, F and G, the nuclei have completely disappeared.   All the cells are markedly pigmented.

CASE 7.—(A136,418, Fig. 285.   Case 4, Ref. 4.)   This reconstruction is from a group of ganglion-cells in the superior cervical sympathetic ganglion of a female twenty-five years of age who had had moderate symptoms of exophthalmic goiter for one year and eight

months, a period of exacerbation lasting three weeks, and then partial relief by double ligation of the thyroid vessels, followed four and one-half months later by thyroidectomy. At autopsy nine days after operation the cervical sympathetic ganglia were noticeably enlarged. Of the 13 cells shown, two, A and B, are apparently normal. Three others, C, D, and E, show normal nuclei but are stained by diffuse pigmentation. Three others, F, G, and H, show normal nuclei, diffuse pigmentation. and in addition masses of heavy pigmentation. One, I, shows diffuse light pigmentation and a partially degenerated nucleus. Two, J and K.
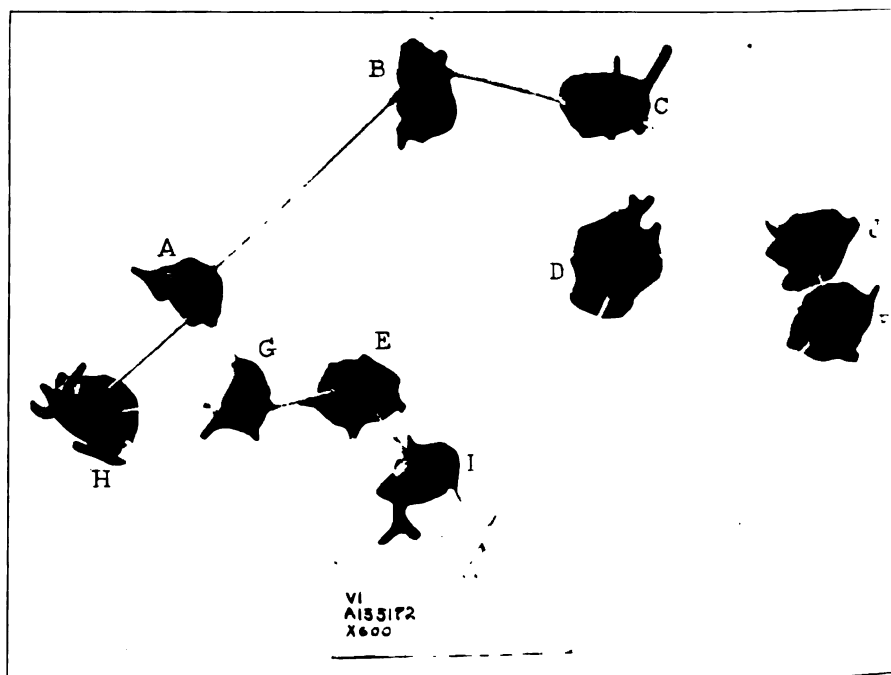
Fig. 286.

show diffuse light pigmentation, masses of heavy pigmentation, and no nuclei. Two, L and M, show complete absence of nuclei.

CASE 8.—(A135,172, Fig. 286. Case 7, Ref. 4.) This reconstruction is from a group of ganglion-cells in the right superior cervical sympathetic ganglion of a female thirty-nine years of age who had had moderate symptoms of exophthalmic goiter for twelve years, with gradual abatement of symptoms for four years. Microscopically the total number of ganglion-cells was apparently much reduced. The condition of those remaining is well represented in the reconstruction. None of the cells are normal. Nine of the ten are heavily pigmented. In the tenth,

J, the nucleus is degenerated. Of the nine pigmented cells, five, A, B, C, D, and E, show quite normal nuclei. One, F, shows a partially degenerated nucleus. In one, G, the nucleus shows advanced degeneration, and two, H and I, are without nuclei.

CASE 9.—(A53,650, Fig. 287. Case 15, Ref. 3.) This reconstruction is from a group of ganglion-cells in the left superior cervical sympathetic ganglion of a female twenty-one years of age who, after a year of suffering from severe symptoms of exophthalmic goiter, had had double ligations of the superior thyroid vessels, followed four months later by removal of the right lobe of the thyroid. Three years and eight
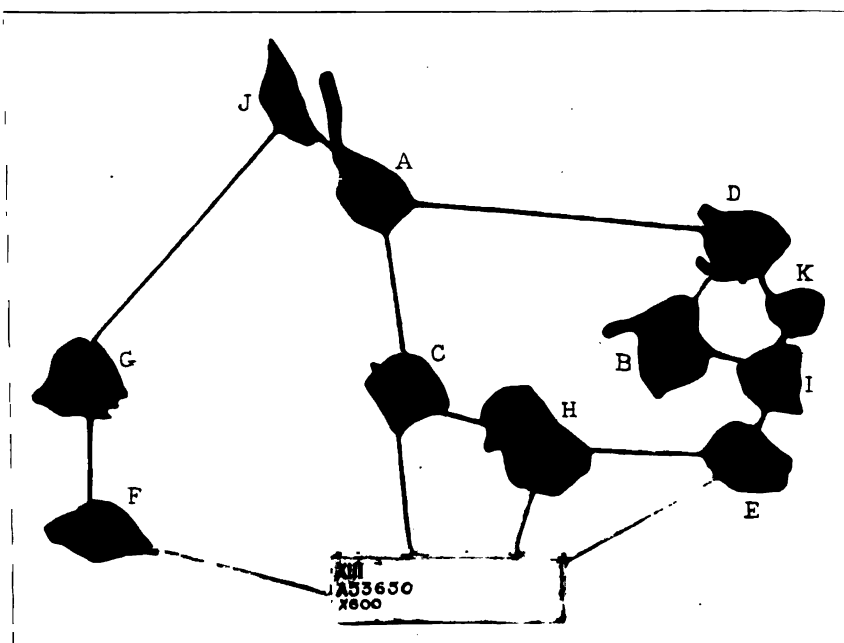
Fig. 287.

months after the removal of her right thyroid her left superior cervical sympathetic ganglion was removed. Examination of sections of this ganglion showed marked diminution in the number of ganglion-cells. Of those which remained, few were normal. In the group of 12 shown, one only, A, is apparently normal. One, B, is normal except for a diffuse light pigmentation. One, C, shows intense local pigmentation but with an apparently normal nucleus. Three, D, E, and F, show similar pigmentation, but with degenerated nuclei. Three, G, H, and I, show pigmentation with complete destruction of the nucleus. Two, J and K, are markedly atrophied, without nuclei and without pigmentation.

DISCUSSION

These reconstructions of groups of ganglion-cells have confirmed the impressions received from the microscopic study of series of sections of ganglia and made it possible to demonstrate their truth beyond a doubt. The material studied is all from patients so young as to preclude the possibility of senility as a factor in the changes observed in the ganglion-cells. The material was all in excellent condition when preserved. The methods of preservation, preparation, and reconstruction eliminate technical artefacts.

A study of the distribution of the cell changes in the groups illustrated shows that in every group there are cells which are apparently capable of function, though in some instances this may be somewhat impaired in all the cells. At the same time in each group there are also cells which are apparently totally incapable of function. These two forms are in close relationship to each other. If we conceive of a distant muscle-fiber or group of thyroid epithelial cells as controlled by a neuron, of which the ganglion-cells of the functioning type are a part, then we must conceive of such muscle-fiber or glandular epithelium as capable of being stimulated and, unless otherwise prevented, of functionating. Conversely, muscle-fibers and glandular epithelial cells receiving their nerve-supply from neurons of which destroyed ganglion-cells are a part cannot receive their stimuli to function through such neurons. Unless another neuron vicariously assumes the function of the one in which the broken link exists, the muscle-fiber or glandular epithelium must perforce go out of commission. The fact that functionating ganglion-cells are in immediate proximity to non-functionating cells is in close harmony with the fact that in exophthalmic goiter we have muscle-fibers and thyroid glandular epithelial cells in advanced stages of degeneration in immediate proximity to others of their kind which are apparently normal. That the changes in the ganglion-cells may be secondary to primary changes in the muscle and glandular epithelium is rendered improbable by the fact that similar changes are not found in cervical ganglia of patients from whom a lobe of the thyroid has been totally removed for many months. Atrophic changes in the ganglion-cells from ablation of the distant organ controlled by neurons of which the ganglion-cells were a part are very different from the granular degeneration seen in cases of exophthalmic goiter. Nor do the changes seen in ganglion-cells of persons of advanced age at all closely resemble those herein illustrated. Indeed, there is every resemblance in the changes in the cervical ganglion-cells in exophthalmic goiter to the changes in the ganglion-cells in the spinal cord in

anterior poliomyelitis and to the changes in the cortical cells of the cerebrum in meningitis. They may best be explained on the hypothesis of a specific primary infection of the ganglion itself.

NOTE ON THE SPECIAL TECHNIC USED IN THE RECONSTRUCTION OF GANGLION-CELLS AT HIGH MAGNIFICATIONS

The reconstructions were made from serial sections of tissue stained by Ramón y Cajal's 1910 silver-impregnation method, and cut at 5 and 10 microns. In all, 18* reconstructions of ganglion-cells were made. Sixteen models were groups of ganglion-cells reconstructed at a magnification of 600 diameters. Five of these were from human tissue removed at operation, eight from human tissue removed at autopsy, two were groups of cells from a goat, and one was of cells from a brook trout. Two models were reconstructions of single human ganglion-cells at a magnification of 3000 diameters. One of these showed a moderately degenerated cell, and the other a practically normal cell with its intracapsular processes and axon.

In making drawings for the above reconstructions at high magnifications variations from the ordinary technic were found necessary. The principal difficulty encountered was that of tracing a single cell in serial sections. The usual method of selecting some definite landmark, such as a blood-vessel, nerve-process, or some particular part of the ganglionic capsule which presented a comparatively uniform appearance throughout the series studied, proved successful for magnifications as high as 600 diameters. With magnifications of 3000 diameters the cell studied covered almost the entire microscopic field, and no identification marks appearing throughout the series could be found. In order then to trace a cell accurately from section to section at this magnification, the entire series was drawn at a low magnification where definite landmarks or guides could be followed, and it was then possible to identify the different sections of a cell at much higher magnifications. When a section of a cell was located at a low magnification, it was exactly centered in the microscopic field, the higher power ocular and objective put in place, and the cell drawn.

The diameters of the normal, or nearly normal, cells were found to vary from 30 to 50 microns. Thus, in 10 microns sections there were 4 or 5 sections to a cell, while in the 5 microns the average was from 8 to 10

* Only 10 are herein shown and described. The others will be published later in relation to other studies.

sections. Cells showing advanced stages of degeneration were sometimes as small as 5 to 8 microns in diameter.

The alinement and transfer of the drawings to wax plates were done with the aid of translucent paper, as described by Kastschenko,[5] so that a single section of a group of cells could be placed in exact registry over the section just proximal or distal to it. On the first section of a group two lines were drawn perpendicular to each other. Several crosses were placed in rather arbitrary relation to these lines. The second section then was fitted accurately over the first section, and these lines and crosses duplicated on it. The same procedure was followed throughout the series. Thus, though there might be a variation in the position of a section of a cell in a series due to an oblique cut, or perhaps to a natural variation, it was still accurately shown by these lines and crosses.

In transferring the drawings to the wax plates the lines and crosses were also transferred. When the wax was cut, the marks were preserved in the form of bridges and guides and, when piled serially in the usual method, wire was substituted for the wax bridges.

In coloring the models the colors used were selected to conform as nearly as possible to the color which each cell stained by the silver-impregnation method. Thus, in a single group, several shades were frequently used. The relative extent and depth of staining of the pigment are indicated by dots on the surface of the models. Each cell, if marked at all, bears a +, 1, or − sign, indicating:

$+$ = Normal nucleus.

1 = Earlier stages of degeneration of the nucleus.

$-$ = Advanced stages of degeneration of the nucleus.

No mark = No nucleus found in any of serial sections of the cell.

The wax plates were made for us in the Anatomic Department of the University of Minnesota through the kindness of Professor Thomas G. Lee.

REFERENCES

1. Cannon, W. B., Binger, C. A. L., and Fritz, R.: "Experimental Hyperthyroidism." Amer. Jour. Physiol., 1914–15, xxxvi, 363–364.
2. McCarrison, R.: Etiology of Endemic Goiter, London, Bale, 1913. Collected Papers on Goiter and Cretinism, Calcutta, Thacker, 1915.
3. Wilson, L. B., and Durante, L.: "Changes in the Superior Cervical Sympathetic Ganglia Removed for the Relief of Exophthalmos," Jour. Med. Research, 1916, xxxiv, 273–296.
4. Wilson, L. B.: "Pathologic Changes in the Sympathetic System in Goiter," Amer. Jour. Med. Sci., 1916, clii, 799–812.
5. Kastschenko, N.: "Methode zur genauen Reconstruction kleinerer makroskopischer Gegenstände," Arch. f. Anat. u. Entwicklungsgeschichte, 1886, pp. 388–393. "Die graphische Isolierung," Anat. Anz., 1887.

THE TREATMENT BY SPLENECTOMY OF SPLE-
NOMEGALY WITH ANEMIA ASSOCIATED WITH
SYPHILIS *

HERBERT Z. GIFFIN

When marked splenomegaly is associated with a history of syphilitic infection or with definitely positive Wassermann tests, a question arises as to the etiologic relationship of syphilis to splenomegaly. It is probable that splenic anemia may occur in a patient who has had syphilis and in whom it cannot be demonstrated that the syphilis is a definite factor in the condition; on the other hand, it would seem quite proper to separate from other forms of splenomegaly those cases in which syphilitic cirrhosis of the liver exists, gummas of the liver are present, or repeated positive Wassermann tests together with other evidence of infection are obtained.

The grouping of cases should be "away from" splenic anemia in order that every endeavor be made to arrive at as accurate a diagnosis as is possible. Cases classified as splenic anemia should quite definitely conform to that syndrome. By carefully distinguishing the other diseases that are associated with splenomegaly our knowledge will be advanced. Hemolytic jaundice, the portal and biliary cirrhoses of the liver, chronic septic splenomegaly, the splenic anemia of infancy (von Jaksch's disease), endothelioid splenomegaly (Gaucher's disease), lymphoma and lymphosarcoma, are the more important entities that have been, and are at the present time, confused with splenic anemia; and in some cases differentiation is impossible even after a study of the pathology. Similarly, cases of splenomegaly in patients with syphilis are to be carefully studied in order that they may be properly classified.

Osler[1] records three cases of syphilis with the picture of the Banti type of splenic anemia. Two of these came to autopsy. One, a boy, aged eleven years, had been under observation for four years before death. A greatly enlarged spleen and a scarred cirrhotic liver containing

several small gummas were found. The patient had had hematemesis and presented nodes on the shin, a syphilitic arthritis, and ascites. The Wassermann test was negative and a secondary type of anemia with leukopenia was present. The second case was that of a woman, aged twenty-two years. A scarred liver, ascites, and a severe anemia were present. There was no history of acquired syphilis, and the case was seen before the days of the Wassermann test. The third case occurred in a man, aged thirty-four years, who came neither to operation nor to autopsy. There was a history of syphilitic infection. A severe anemia was present, the liver seemed to be fissured, and the spleen extended to the level of the iliac spine.

Anderson,[2] Caussade and Levi-Franckel,[3] and Queyrat[4] have reported in all three additional cases simulating the Banti type of splenic anemia. These patients were all definitely syphilitic. None of them was operated on, but one came to autopsy.

Diffuse, *non-gummatous hypertrophy* of the spleen quite frequently occurs in patients with syphilis. In adults it is often associated with gummas of the liver or a definite cirrhosis. *Gummas* of the spleen may be miliary or solitary in character. *Gummatous cicatrices* cause a greatly enlarged organ, and *amyloid spleen* has been found in chronic cases. Moxon[5] has reported a case of *acute splenitis* associated with syphilitic pneumonia, a finding which is evidently exceedingly rare.

Enlargement of the spleen in early syphilis is probably quite common. Wile and Elliott,[6] in a review of 100 cases of early syphilis, found 36 with palpable spleens. In none of these cases was enlargement of the liver present. Splenic enlargement in early syphilis usually tends to disappear, but may persist longer than any other visceral manifestation.

Syphilitic splenomegaly during the first eighteen months of life, and especially during the first three months, is common. From two years to twelve years of age undoubted cases are relatively rare. Up to the age of six months splenic enlargement appears in 40 per cent. of syphilitic babies. Carpenter,[7] in a review of 348 cases of splenomegaly in infants and children under twelve years of age, found 57 cases of undoubted syphilis with enlargement of the spleen. He concluded that syphilis was second only to rickets as a cause of splenomegaly in infancy.

Hutchinson,[8] in a report of 22 cases of splenic anemia of infancy (von Jaksch's disease), found 4 with congenital syphilis. Weller,[9] in a report of 30 cases of the splenic anemia of infancy, found 8 to be syphilitic. Syphilis in infants may be associated with blood findings

similar to those of the splenic anemia of infancy, just as in adults it may be associated with blood findings similar to those of the adult type of splenic anemia. This difference in the blood picture is probably due to a peculiar reaction of the infant's hematopoietic system to disease (Giffin[10]).

Gummatous affection of the spleen is very rare in children and extremely rare in infants. It is usually associated with gummas elsewhere. Still[11] collected 4 cases from the literature and reported 2 cases of his own.

In adults, gummas of the spleen are also of rare occurrence. Still,[11] in 1897, was able to collect only 21 cases from the literature. Martin[12] reported a case in which two or three small gummas were found in the spleen in association with multiple gummas throughout the liver and a marked anemia. It is probable, however, that careful examination of the pathologic tissue would show a somewhat greater frequency for gummas of the spleen in adults than now appears on a study of the literature.

It is a striking fact, nevertheless, that in adults as well as in children syphilitic splenomegaly is most frequently of a diffuse, non-gummatous character. It is also well known that syphilitic splenomegaly may persist or recur in spite of the most active antisyphilitic treatment. Moreover, the severe secondary type of anemia that is frequently present in these cases may not improve with medical treatment. Because of these facts, splenectomy has been performed in three recorded instances and the results would seem to have justified the procedure.

Coupland,[13] in 1886, reported a case of splenectomy for syphilitic spleen. Two years after operation the patient died following hematemesis. Ascites had been present. Autopsy revealed a scarred liver quite typically syphilitic. Hartwell[14] (1913) performed splenectomy on a patient with a severe anemia of the secondary type and a history of hematemesis. The patient denied the possibility of syphilitic infection, but a Wassermann test was strongly positive. Neosalvarsan, mercuric salicylate, potassium iodid, iron, and arsenic had been administered while the patient's condition became less satisfactory. Splenectomy was followed by very prompt improvement. In two weeks the hemoglobin had risen from 25 to 80 per cent. Pathologically the trabeculæ were thickened and large and numerous follicles having fibroid centers were present. Mention of gummas was not made. French and Turner[15] (1914) removed a spleen measuring 7 x 5 inches, and weighing 18 ounces, from a boy aged five years, in whom there was a blood-count suggestive of the splenic anemia of infancy. A Wassermann test had been positive

several times and the patient had received antisyphilitic treatment with no benefit. The patient was apparently well in two months.

In a general review of 58 cases of splenectomy in the Mayo Clinic (July, 1915) 2 cases were briefly discussed in which marked splenomegaly was associated with syphilis (Giffin[16]). One additional patient has been operated on since that time. The histories of these three patients would seem to be of sufficient importance and interest to justify detailed discussion.

CASE 1 (A119,102) (Fig. 288).—*Marked splenomegaly; severe anemia; no hematemesis; history of syphilitic infection not obtained; Wassermann, total inhibition; antisyphilitic treatment without definite improvement; splenectomy; treponemas in walls of splenic vessels; excellent health one year later.*—G. H. I., woman, aged forty years; married. First examined November 14, 1914. The family history was negative. She had been married fourteen months and had not been pregnant. She had had catarrhal jaundice at the age of eleven years, typhoid fever at the age of twenty-eight years, and had suffered from many attacks of tonsillitis and quinsy. She stated that her spleen had been enlarged since the typhoid fever twelve years before; that since that time she had been pale and her complexion had been sallow. As a child, up to the age of fifteen years, she had had an occasional attack of upper abdominal
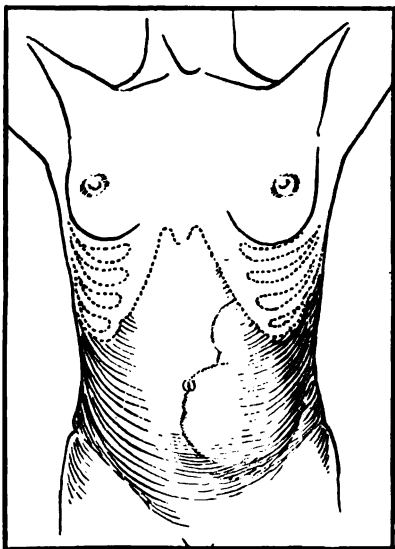
Fig. 288 (A119,102).—Position and contour of spleen. Splenomegaly associated with syphilis.

colic without chills, each attack lasting for an hour or two. Four weeks before examination she had suffered from a severe attack of pain in the region of the epigastrium and right costal margin, and was slightly jaundiced after this. There was no history of hemorrhage nor dyspnea, and the patient felt quite strong. There had been a little edema; gastro-intestinal and urinary symptoms were absent. About one year previous to examination a tender swelling had appeared over the anterior portion of the left chest. This was lanced, and later several small pieces of bone were discharged. Six months previous to examination at the Clinic the rib was curetted, but drainage had continued up to the time of examination. Antisyphilitic treatment had been administered for six months.

Physical examination disclosed a thin, pale woman; the skin showed a lemon-yellow tint. The weight had been reduced in one year from 130 to 103 pounds. There were small discharging sinuses found in the area of the fifth and sixth left chondrocostal junctures. A large tumor which could easily be recognized as spleen filled almost the entire left half of the abdomen and extended beyond the navel and almost to the symphysis. It was apparently low in position, as its upper pole could be palpated below the left costal margin. The liver seemed to be slightly enlarged on percussion. Examination of the urine was practically negative. The systolic blood-pressure was 106 and the diastolic blood-pressure was 70. Examination of the blood showed a secondary type of anemia, with the hemoglobin at 38 per cent. Red-blood cells numbered 2,950,000 and showed slight anisocytosis. The leukocytes were 6650, and a differential count was not abnormal. Evidence of tuberculosis was not present. A von Pirquet test was negative, and roentgen examination of the chest revealed no pulmonary lesions. A Wassermann test showed total inhibition. On account of the great enlargement of the spleen, and because of the fact that active antisyphilitic treatment had proved unsatisfactory, splenectomy was advised.

Operation, December 4, 1914 (W. J. Mayo).—A large spleen measuring 12 x 7 inches, and adherent to the diaphragm, stomach, liver, and pancreas, was removed through a long left incision. The tail of the pancreas extended up to the hilum of the spleen so that a dissection of about 4 inches had to be made. The left lobe of the liver was moderately adherent to the abdominal wall, but there was no evidence of cirrhosis. The patient had an uninterrupted convalescence and left the hospital on the eleventh day.

Pathologic Report (L. B. Wilson).—Weight of spleen, 900 grams; gland normal in contour, with very marked notch and dorsal groove; external surface slightly nodular; considerable perisplenitis; on section, organ is firm, tough and very dark colored. Microscopically there is a diffuse fibrosis with a moderate lymphocytosis; pulp 3; lymphoid tissue 3; reticulum 3; endothelium of sinuses 2; atrophic pigment 1; amyloid degeneration 0; arteriosclerosis 3; adventitia of arteries markedly affected, in some cases amounting to typical gummas; numerous treponemas in vessel-walls.

Postoperative Condition.—One year after operation the patient's physician stated that she had gained much strength, 15 pounds in weight, and was feeling well. Her blood count was as follows: Hemoglobin, 80 per cent.; erythrocytes, 3,552,000; leukocytes, 11,000. The differential count was not abnormal.

In this case a history of syphilitic infection was not obtained, but a Wassermann test showed total inhibition. The patient was aged forty years, had been married fourteen months, and had not been pregnant. The spleen was very large and a severe anemia of the secondary type without leukocytosis was present. The liver was not cirrhotic;

there had been no hemorrhages. Antisyphilitic treatment had been attended with unsatisfactory results, while splenectomy was followed by prompt improvement and excellent health one year later.

CASE 2 (A125,899, Fig. 289).—*Moderate splenomegaly; marked anemia of the secondary type without leukocytosis; liver contained palpable gummas; no hematemesis; negative history of lues in both patient and husband; Wassermann test, total inhibition; no improvement of anemia on antisyphilitic treatment; splenectomy; prompt improvement in general health and blood.*—H. S. D., a woman, aged thirty-two years; married; was first examined March 6, 1915. The family history was negative. For the last ten years menstruation had occurred irregularly, from one week to three months apart. Several hemorrhages occurred which her physician had interpreted as miscarriages. She had had scarlet fever at nine years of age, pneumonia at eighteen years; frequent attacks of tonsillitis as a child. Tonsillectomy had been done at the age of fifteen years. The patient complained chiefly of upper abdominal pain and profuse and irregular menstruation. She had been more or less of an invalid for ten years. Her complaints had been quite varied and often of an obscure character. There was a history of chills at frequent intervals. She had taken large quantities of quinin, but plasmodia had never been demonstrated in the blood. There had been frequent attacks of bronchitis, with evening fever

Fig. 289 (A125,899).—Position and contour of spleen and liver. Splenomegaly associated with syphilis.

and night-sweats, and she had been treated for tuberculosis, although there had never been positive evidence of this disease. For seven or eight years a cramping of the muscles had recurred in various parts of the body at frequent intervals. For the past five or six years soreness and tenderness had been present in the upper abdomen, at times causing considerable complaint and being aggravated by pressure. She had never had an acute abdominal colic. The sensitiveness over the upper portion of the abdomen had been more pronounced for six months prior to examination. She had not known that the liver and spleen were enlarged.

Physical Examination.—The patient was moderately thin and anemic. Examination of the heart and lungs was negative, and stereoscopic plates of the lungs failed to disclose any evidence of tuberculosis.

The liver extended 2 inches below the right costal margin, and hepatic dulness measured about 6 inches in the right mammillary line. In the epigastrium two irregular masses could be seen to move downward with respiration. These were easily palpable and apparently located in the liver. The spleen was enlarged to the level of the navel and its surface was smooth; splenic dulness measured 9 x 17.5 cm. Abdominal fluid did not seem to be present. There was extreme tenderness to palpation over the entire upper abdomen. Examination of the urine was negative. The systolic blood-pressure was 126 and the diastolic 86. An examination of the blood showed a hemoglobin percentage of 50. The red-blood count was 4,090,000; the leukocyte count 6200; the differential count was not abnormal. A Wassermann test showed total inhibition and was repeated with a positive result.

The patient remained under observation for one month, during which time she received three injections of neosalvarsan, and mercurial inunc-tions and potassium iodid. She gained somewhat in strength and 7 pounds in weight. The hemoglobin, however, remained low (58 per cent.), and the size of the spleen was not reduced although the liver seemed to be smaller.

Operation.—Splenectomy was decided upon and performed April 1, 1915, by W. J. Mayo. A spleen weighing 670 grams, and measuring 9 x 6 inches and quite adherent, was removed through a left lateral incision. There was a small amount of free fluid present in the abdomen. The liver showed extensive cirrhosis. Gummatous tumors were present and the liver was divided into large lobes by irregular contractions. The liver was approximately three-fourths normal size. The tumors were typically gummatous in character, and one the size and shape of a gall-bladder was present in the left lobe.

Pathologic Report (L. B. Wilson).—Weight of spleen, 670 grams; gland long and slender; no notch; slightly roughened surface; considerable perisplenitis; on gross section organ is pale and firm, but not tough. Microscopically there is a moderate diffuse fibrosis; pulp, 2; lymphoid tissue, 2; reticulum, 3; endothelium of sinuses, 2, swollen; pigment, 0; small amount of amyloid degeneration; arteriosclerosis, 2.

Postoperative Course.—Recovery from the immediate operation was uneventful, and the patient was discharged from the hospital on the twelfth day. Eight months after operation she had improved markedly in weight and strength and the anemia had disappeared.

This patient presented a very irregular and indefinite history. Positive evidence of luetic infection could not be obtained, but the Wassermann tests were strongly positive. The spleen was moderately enlarged and non-gummatous. The liver contained palpable gummas. The anemia was marked and of a secondary type without leukocytosis. There was no history of hemorrhages. Active antisyphilitic treatment for one month caused no improvement of the anemia, while splenectomy was followed by very definite improvement.

'16—39

Case 3 (A140,128, Fig. 290).—*History of syphilitic infection at twenty-one. Three positive Wassermann tests elsewhere during the last two years; Wassermann test negative at the time of examination; moderate splenomegaly; slight anemia; recurrent hematemesis; long-continued antisyphilitic treatment attended with only partial relief; splenectomy. One gumma and a few treponemas in spleen; excellent condition three months later.*—H. P., male, aged thirty-five years; single. Examined September 2, 1915. Family history negative. The patient had had a preputial sore at the age of twenty-one and three attacks of gonorrhea. There was a negative history for other severe diseases. Six years previously he had been jaundiced for two months and he thought the skin had never entirely cleared after that time. He had gradually lost weight from 210 pounds to 170 pounds, and had not had his former good general health. Two years previous to examination an ulcer had formed on the right shin. A large spleen and a very large liver were discovered two years before examination. The hemoglobin was 60 per cent. At that time he was complaining of left-sided headache, usually worse from 4 to 10 p.m.; pain in the left arm and left leg. Several nodules formed in the left frontal region. From one to three times a week he had severe chills. One and a half years previously the pain in the head, arm, and leg was so severe that morphin was necessary. At this time there was an effusion into the right knee-joint. Salvarsan was given; about two days later a severe attack of hematemesis resulting in unconsciousness occurred; after recovery from this the pain had disappeared. Since that time salvarsan intravenously and mercury intramuscularly had been administered. His general health was then quite good until eight months before examination, when a second severe gastric hemorrhage occurred. This had been followed every two or three weeks by nausea and black stools.

Fig. 290 (A140,128).—Position and contour of spleen. Splenomegaly associated with syphilis.

Physical Examination.—The patient was well nourished and weighed 173 pounds. The left frontal region of the skull was irregularly depressed. The spleen filled the entire left upper quadrant of the abdomen and was smooth; liver dulness was apparently not increased. A notch of the spleen was palpable while the edge was indefinite. Scars were present

on the right shin. Examination of the urine was negative. The systolic blood-pressure was 118 and the diastolic 72. Examination of the blood showed a hemoglobin of 85 per cent.; red-blood count of 4,240,000; leukocytes, 4900; differential count was not abnormal; coagulation time was five minutes. Test-meal showed slight hyperacidity. Fluoroscopic examination of the stomach presented evidence suggestive of duodenal ulcer (duodenum was negative at operation); Wassermann test was negative. Three positive Wassermann tests had been obtained elsewhere during the last two years.

The physician who referred this patient stated that while his Wassermann test had become negative and he had improved to a considerable extent under salvarsan and mercury, on the other hand improvement reached only a certain point and then his recovery seemed to be at a standstill. (I am indebted to H. B. Anderson, of Toronto, for complete notes on this case.)

Operation.—Splenectomy was decided upon and performed September 13, 1915, by D. C. Balfour. A spleen five times normal size was removed through a left lateral incision. The liver was small and deeply fissured, so that portions of the organ appeared almost like separate masses. There was marked obstruction of the portal circulation, as evidenced by the varicosities in the round ligament. Stomach, duodenum, and gall-bladder were negative.

Pathologic Report (L. B. Wilson).—Weight of spleen, 1050 grams; notch distinct, capsule slightly thickened; on section, firm, tough, hard, showing general fibrosis. Microscopically there is an intense diffuse fibrosis, 3; pulp, 2; lymphoid tissue, 1; reticulum, 4; endothelium of sinuses, 2; pigment, 1; amyloid degeneration, 2; arteriosclerosis, 3; affecting principally adventitia; 1 typical gumma near vessel, involving wall; a few treponemas.

Postoperative Condition.—The postoperative course was uneventful save for the appearance of a rather severe capillary bronchitis beginning on the sixth day. As a result of the coughing a resuturing of the abdominal wound was necessary two weeks after operation. The patient was discharged in satisfactory condition four weeks later. A Wassermann test done six weeks after operation was negative. Three months later the patient was in excellent condition, with hemoglobin at 90 per cent.

This patient presented a history of syphilitic infection, and during the course of his illness had had three positive Wassermann tests. There had been two attacks of severe hematemesis. Marked splenomegaly and an advanced cirrhosis of the liver, apparently syphilitic, were present. The anemia had been recurrent. Very prompt improvement followed splenectomy.

The three cases of splenomegaly herewith reported are definitely associated with lues. Cases undoubtedly occur, however, in which a luetic history is obtained which seems to have no etiologic relationship

to the splenomegaly. As an instance of this occurrence the following brief abstract may be given:

CASE 4 (A89,075).—*N. B. S., man aged thirty-five years; married. Examined August 3, 1913; definite history of syphilis with secondaries ten years previously; onset of present illness sudden, with severe hematemesis six weeks previous to examination; recurrence of hematemesis ten days before examination; a third hemorrhage nine days before examination; hemoglobin 35 per cent.; secondary type of anemia; erythrocytes, 2,410,000; leukocytes, 4900. Marked enlargement of the spleen; ascites; gradual improvement followed by splenectomy.*—A spleen measuring 10 x 9 inches and weighing 1030 grams was removed. Microscopically there was a diffuse hypertrophic fibrosis. The liver was of normal size and showed no evidence of syphilitic cirrhosis.

This patient presented a definite history of syphilis followed by active treatment and apparent cure. Ten years later sudden severe hematemesis occurred. Marked splenomegaly with ascites was found. A severe secondary type of anemia and negative Wassermann tests completed the typical clinical picture of splenic anemia of the Banti type. At the time of operation no evidence of syphilitic cirrhosis was found.

SUMMARY

1. It is probable that the syndrome of splenic anemia and Banti's disease may be present in a patient who has had syphilis, and in whom it cannot be demonstrated that the syphilis is a definite etiologic factor in the condition.

2. Cases of marked splenomegaly in which syphilitic cirrhosis of the liver or gummas of the liver are present, or in which repeated positive Wassermann tests, together with other evidence of infection, are obtained, should be separately classified and studied.

3. Because of the fact that syphilitic splenomegaly with secondary anemia has persisted in spite of active antisyphilitic treatment, splenectomy has been done elsewhere in three recorded cases. Three additional cases of this character are herewith reported.

4. The results following splenectomy for marked splenomegaly associated with syphilis and anemia performed after a trial of antisyphilitic treatment seem to have justified the procedure in these few instances.

5. The three cases herewith recorded showed prompt improvement after splenectomy and were in excellent condition three months, eight months, and one year respectively from the date of operation.

REFERENCES

1. Osler, Wm.: "Syphilis of the Liver with the Picture of Banti's Disease," Clin. Jour., 1914, xliii, 462–464.
2. Anderson, H. B.: "Case of Syphilitic Splenomegaly Resembling Banti's Disease," Canada Lancet, 1914, xlvii, 740–742.
3. Caussade, G., and Levi-Franckel, G.: "Un cas de syphilis ayant evolué sous la forme du syndrome de Banti; le syndrome de Banti," Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, xxxvii, 1029–1047.
4. Queyrat, L.: "Syndrome de Banti et syphilis," Bull. et mém. Soc. méd. d. hôp. de Paris, 1914, xxxviii, 296–299.
5. Moxon, W.: "Case of Acute Splenitis (?) in a Syphilitic," Tr. Path. Soc., London, 1871, xxii, 274–276.
6. Wile, U. J., and Elliott, J. A.: "A Study of Splenic Enlargement in Early Syphilis," Amer. Jour. Med. Sci., 1915, c, 512–518.
7. Carpenter, G.: "Splenomegaly in Infants and Young Children," Brit. Med. Jour., 1903, ii, 463–469.
8. Hutchinson, R.: "Some Disorders of the Blood and Blood-forming Organs in Early Life," Lancet, 1904, i, 1323–1333.
9. Weller, C. V.: "Splenic Enlargement in Infancy and Childhood," Arch. Pediat., 1914, xxxi, 514–524.
10. Giffin, H. Z.: "Splenectomy for Splenic Anemia in Childhood and the Splenic Anemia of Infancy," Ann. Surg., 1915, lxii, 679–687.
11. Still, G. F.: "Gumma of the Spleen in Children," Tr. Path. Soc. Lond., 1897, xlviii, 205–209.
12. Martin, W.: "Case of Syphilitic Splenomegaly," Med. Rec., 1914, lxxxv, 593.
13. Coupland, S.: Brit. Med. Jour., 1886, i, 1445.
14. Hartwell, J. A.: "Splenomegaly with Anemia in a Syphilitic Patient," Med. Rec., 1914, lxxxv, 593.
15. French, H., and Turner, P.: "Case of Splenic Anemia Treated by Splenectomy (Syphilis)," Proc. Roy. Soc. Med., 1913–14, vii, Clin. Sect., 77–78.
16. Giffin, H. Z.: "Clinical Notes on Splenectomy," Ann. Surg., 1915, lxii, 165–170.

INDICATIONS FOR SPLENECTOMY IN CERTAIN CHRONIC BLOOD DISORDERS: THE TECHNIC OF THE OPERATION*

DONALD C. BALFOUR

Splenectomy has already proved a curative measure in certain diseases associated with definite blood changes, and the operation has recently been advocated for other diseases which appear to be more or less closely related to those in which the spleen is now the known causative factor. The basis on which splenectomy has been suggested in these heretofore incurable conditions will be more clearly understood if we briefly review the development which has resulted in the present situation.

Splenic anemia offers the most familiar example of the therapeutic value of splenectomy. Sufficient time has now elapsed since the earlier operations for this disease to prove that the results of splenectomy in early or in moderately advanced cases are not only excellent, but permanent. The most interesting characteristic of the disease as concerns the purpose of this paper is its tendency to develop cirrhotic changes in the liver. In fact, Banti described the disease as it appeared in its later stages when it is associated with marked cirrhosis and with ascites. In such a stage, from a diagnostic standpoint, it is often difficult and sometimes impossible to determine in a given case whether the condition is the result of a true splenic anemia or of a primary liver cirrhosis associated with a large spleen. Experience has shown that in the very late stages of splenic anemia definite improvement following splenectomy cannot be expected, yet it is also true that a moderate cirrhosis, even associated with ascites, has been present in some cases in which excellent results have been obtained. This fact, therefore, with the probability

that certain of the cases which have been classified as true splenic anemias and operated upon on that diagnosis, were in reality cases of primary cirrhosis, was responsible for the suggestion that splenectomy might prove of value in arresting the progress of selected types of hepatic cirrhosis.

The interdependence of spleen and liver is not clearly understood, yet there is ample evidence to show that some of the most important functions of the liver, for example, its hemolytic power, are more or less controlled by the spleen. Certain pathologic conditions in the liver, therefore, are the result of overactivity, which may in turn be due to overstimulation by the spleen.

During the last two years, with this theory as a basis, selected patients with primary hepatic cirrhosis have been splenectomized. Two, at least, of four such cases of our own gave promise that the removal of the spleen might stop or retard the progress of the disease, but we are not yet in a position to state the value of such a procedure.

The success of splenectomy in splenic anemia, with associated splenomegaly and severe anemia, has led to splenectomy in other diseases in which splenomegaly and anemia are characteristics. One of the most interesting of these is the syphilitic spleen; we have seen good results follow splenectomy in three cases of this form of syphilis. The prominent clinical features of the cases in which we believed operation to be indicated were: (1) Splenomegaly; (2) a history of syphilis not responding to treatment; (3) positive Wassermanns; (4) anemia. It is important to note that previous to operation a negative Wassermann could be obtained under appropriate treatment, but the reaction became positive as soon as treatment was discontinued. All these patients had gummas in the liver, and in the spleens removed the spirochete could be demonstrated in large numbers. It was also a clinical observation that although the virulence of the infection could be more or less controlled by antisyphilitic treatment, it was not eradicated.

From the foregoing facts the conclusion may be drawn that the spleen picks up the spirochetes and harbors them, and this conclusion is supported by the surgical observation that removal of the spleen, followed by antisyphilitic treatment, results in prompt and permanent relief.

The influence which the spleen exercises on the hemolytic function of the liver and spleen is most strikingly illustrated in the effect of splenectomy in hemolytic jaundice. Although this disease is a problem from an etiologic standpoint, the most important therapeutic fact is that

splenectomy is followed by prompt, complete, and permanent cure. The rapid disappearance of the icterus, which is the most obvious symptom of the disease, is an amazing clinical result; the anemia, which is sometimes severe, is also rapidly corrected.

The remarkable results following splenectomy in splenic anemia and hemolytic jaundice, particularly the latter, appear to have provided the basis on which Eppinger and others have suggested that similar surgical treatment might prove of value in pernicious anemia. It is important, therefore, that the relationship of splenectomy to these other diseases should be borne in mind. The argument becomes more forceful if it is possible to establish similarities between any one of these diseases for which splenectomy is curative, and pernicious anemia. Many of the features of hemolytic jaundice appear to have a counterpart in pernicious anemia, and, in fact, Eppinger believes that the chief, and possibly the only, difference between hemolytic jaundice and pernicious anemia is that in the former the bone-marrow is able to compensate for the increased blood destruction, whereas in pernicious anemia it soon loses this power, and the disease eventually is dependent on a bone-marrow disability.

It would, therefore, appear as a logical sequence that since splenectomy has proved a specific in hemolytic jaundice, it would sooner or later be advocated in pernicious anemia. Although the first operations for this disease were performed, both abroad and in this country, about the same time (1913), to Eppinger must be given special credit for efforts to establish a scientific basis for the surgical treatment. While the surgical therapeusis of pernicious anemia can be considered as on trial, it presents features of much interest and promise, and splenectomy is now being performed with a frequency which should soon permit definite and decisive deductions.

It must, of course, be primarily recognized that any new therapeusis in a disease of the character of pernicious anemia must be subjected to a particularly thorough trial. The extreme chronicity of the disease in its usual course, and the fact that, with or without treatment, remissions occur during which the patient is much improved and the blood may even revert to normal, stamp any conclusions based on the early results of operation as premature. This much, however, can be said, that immediate improvement follows splenectomy more consistently and promptly than any treatment heretofore used.

It is on the ultimate results, however, which are as yet insufficient,

that the final decision as to the real efficiency of splenectomy in pernicious anemia must rest.   There is at the present time, therefore, decided uncertainty as to any superior therapeutic value of a permanent character possessed by splenectomy.   It is also true that pernicious anemia has thus far been an incurable disease, ranking in fatality with cancer and less amenable to successful treatment.   The certainty of the ultimate prognosis has been the outstanding feature of our knowledge of the disease, and the doomed patient could hope only that the disease would be slowly progressive and not associated with great physical disability.

The pathologic picture which Eppinger has described as distinctive of the spleen in pernicious anemia is as follows: The pulp areas in the spleen, and only these, are gorged with blood.   Eppinger explains this engorgement as a direct result of an abnormal condition of the central artery.   It has been shown that the entire wall of this artery is greatly thickened, and that the greatest change takes place in the media.   The theory is, briefly, that sufficient obstruction results to force the flow of blood through the capillaries into the pulp areas, where the erythrocytes are destroyed.   If a constant pathology can be demonstrated in the spleen in pernicious anemia, it will be a great advance toward the rational treatment of the disease.

While it cannot be held that the basis on which Eppinger and his followers have endeavored to establish the surgical treatment of the disease has been confirmed or even well supported by others, it is not essential, nor is it good judgment, to postpone surgical treatment of the disease until an acceptable basis for such treatment is generally recognized.

The hemolytic nature of pernicious anemia is demonstrated by the increased amounts of urobilin and urobilinogen excreted.   It has been assumed, and there is much clinical and experimental evidence to show, that this hyperhemolysis is due to a hypersplenism, and interesting investigations are now being conducted, after the suggestion of Schneider, to determine the exact quantity of these hemolytic products by obtaining them immediately with a duodenal tube on their exit from the liver. Giffin has shown, by the records of the urobilin and urobilinogen estimation in a series of cases of pernicious anemia, that the values appeared to run more or less parallel to the degree of icterus, and that in some cases at least there was a marked fall in the value of the blood-derived pigments after splenectomy.   It is possible that from this method information of at least prognostic value may be derived.   Giffin has suggested

the very interesting possibility that the relation of hemolysis, as shown by the estimation of the blood-derived pigments and the bone-marrow disability, as illustrated by the blood picture, may result in deductions of decided value.

The effect of splenectomy in other diseases being the primary basis for the operation in pernicious anemia, the further indications must be mainly based on operative results, and as early results only are as yet available, such indications are presented with reservation and will undoubtedly be subject to further modification.

INDICATIONS FOR OPERATION

Size of Spleen.—It would appear that the larger the spleen the better the prospects that splenectomy will prove of benefit. It may be assumed in this disease that oversize means overactivity, and it has certainly been true, in our own experience, that the most consistently promising results following splenectomy have occurred when the spleen showed the greatest enlargement. However, good immediate results have been obtained also when little or no enlargement was present. The palpability of the spleen, therefore, has been looked on as one of the first considerations in discussing the advisability of splenectomy. Exclusive of three cases in which the spleens were very large, the spleens in a series of 37 of our cases averaged 400 gm., as compared with the normal of about 195 gm. It should be remembered that any estimation of the size of the spleen before it has become actually palpable is rather speculative. W. J. Mayo early pointed out that frequently in exploring the spleen in the course of abdominal operations, and comparing its actual size with that noted in the clinical records, it is found that clinical records are not consistently correct and as a rule are accurate only when the organ is palpable.

Icteric Types of the Disease.—The very intimate relationship between the spleen and the acholuric icterus as seen in pernicious anemia, hemolytic jaundice, and in hypertrophic cirrhosis is proved both by operative results and experimental studies. The remarkably rapid, complete, and permanent disappearance of the jaundice in hemolytic jaundice, for example, following splenectomy is sufficient evidence of the splenic factor. Experimentally, it is very difficult to produce toxic jaundice in spleenless dogs by those poisons which readily produce it in the normal dog. In spleenless dogs under the administration of such poisons (particularly toluylendiamin) the bile remains thin and green, while in non-splenec-

tomized dogs it becomes viscid. Stadelmann was the first to attribute such acholuric jaundice to this thickening of the bile, which delays, by very reason of its viscosity, its own passage through the finer bile capillaries. A marked icteric discoloration in the skin in pernicious anemia may be taken as an indication that the spleen is to a large degree responsible for the abnormal blood destruction feature in the disease.

Response to Transfusion.—The transfusion of blood, particularly of small quantities at frequent intervals, has for some time been recognized as valuable treatment, though only of temporary character, in pernicious anemia. It has recently become evident, however, that transfusion is not only an excellent therapeutic expedient, but that in the immediate response following the procedure it is of distinct prognostic value in foretelling the probable results of splenectomy. Definite improvement after transfusion is a strong indication for splenectomy, but when no benefit occurs from repeated transfusions, splenectomy will probably also prove futile, though the reverse of both these indications is occasionally true. Transfusion seems to serve a double purpose, as does the ligation of the blood supply in exophthalmic goiter, by (1) improving the condition of the patient, and by (2) predicting rather accurately the effect of the major operation on the disease.

Duration of the Disease.—Although in our own experience satisfactory results may be obtained when the disease has been of long standing, we believe the results are not so favorable as those in cases in which the disease has existed a short time.

Radical measures to interrupt the progress of the disease while it is yet in an early stage seem logical. Although there is little positive knowledge as to the reason for the permanent disability of the bone-marrow, it is probable that it is constantly overstimulated in an effort to meet the abnormal demands made on it, and also suffering from the influence of the hemolytic agent or some other toxin.

In pernicious anemia, like exophthalmic goiter, the course of the disease tends to be interrupted by periods of comparatively good health and normal bodily functions. Each recurrence, however, further damages the organs which are affected by the toxin, and although with the interruption of the process in its early stages there may be complete restoration to health, sooner or later, regardless of the further course of the disease, permanent injury results.

The ability of man to develop other hematopoietic centers, when the normal source of the supply of blood-corpuscles, the bone-marrow, is under great stress, is well known. Such centers have been demonstrated

in the spleen, the liver, and lymph-nodes. Whether in pernicious anemia the augmentation of the hematopoietic functions is simply compensatory by reason of the increased blood destruction of the disease, or whether the bone-marrow, under the influence of some specific toxin, is primarily diseased, so that immature red cells are put into the circulation, is as yet problematic. It is more than possible that pernicious anemia, like cancer, could be cured in its inception, if treated properly; when it is well established, a vicious circle is produced and a permanently disabled hematopoietic system is added to the primary etiologic factor or factors. The question of permanent cure in pernicious anemia, therefore, may ultimately depend, not only on interrupting the progress of the disease by removing what appears to be the primary factor, but also to a greater extent on our ability to restore the bone-marrow and other hematopoietic structures to their normal physiologic functions. It is to be hoped that earlier recognition of pernicious anemia will result in earlier splenectomy.

Activity of the Disease.—The activity of the disease is an important consideration in discussing the advisability of operation. Splenectomy should be undertaken with hesitation in acute stages of pernicious anemia and especially with a falling blood-picture. The operation cannot at the present time be advocated when cord changes and other permanent pathologic processes mark the terminal stages of the disease. Moreover, as already suggested, if it is not possible to tide a patient over the critical periods by transfusion, splenectomy is contraindicated. Definite statements based on the qualitative blood-picture cannot be made, but if the hemoglobin is under 25 per cent. and cannot be raised, operative treatment is of considerable risk and has doubtful results.

The extent of the disability of the patient must, of course, be carefully considered. If a patient with every evidence of the disease is able to carry on his usual occupation, splenectomy cannot be strongly advocated, yet these may be the very patients in whom good results may be obtained. The operation may be urged more legitimately when the patient is unable to do his work or is a chronic invalid.

A positive diagnosis of pernicious anemia having been made and the advisability of splenectomy established, it is important that the patient and his family be correctly informed as to the purpose and the status of splenectomy.

Splenectomy we have found of less technical difficulty in pernicious anemia than in any other disease or condition. An incision toward the outer edge of the left rectus extending above to about one inch from the costal margin and below to the level of the umbilicus is satisfactory. An

abdominal exploration should first be made, especially in view of the frequent complications of liver and gallbladder met with in those diseases for which splenectomy is advocated.

The dislocation of the spleen from its position against the diaphragm and against the left kidney is not, as a rule, complicated by formidable adhesions in pernicious anemia; nevertheless, the operation is facilitated and the minor oozing points are controlled by the introduction of a large abdominal pack against the newly exposed surface. In the actual removal of the spleen it must always be borne in mind that the stomach and pancreas are in close anatomic relationship. The fundus of the stomach is in such immediate apposition to the gastric surface of the spleen that its wall may be injured if the gastrosplenic omentum at this point is not divided with particular care.

The tail of the pancreas does not bear a constant relationship to the splenic pedicle. In some instances it lies in front, in others behind, and it may extend along the pedicle until its tip rests in the hilus of the spleen. It is quite evident, in certain cases, that the tip of the pancreas must be dislodged from its position if the pedicle is to be ligated without injury, although such a condition is relatively unusual in pernicious anemia. The pedicle is rarely of sufficient size to present any difficulties in its control. It is comparatively easy to isolate the artery and the veins and ligate them independently. Although it has been advised that the artery should be ligated first in order that the spleen may empty itself of its blood, and although I have done this in some cases, I have never been able to observe any difference in the convalescence or the effect of splenectomy on these patients as compared with those in whom the artery and veins were ligated at the same time.

All bleeding points having been securely controlled, the pack is removed and the diaphragmatic surface inspected.

Summary

We believe that splenectomy should be considered in every case of pernicious anemia in which the diagnosis has been established and all possible etiologic factors which might be independently remedied have been excluded. The failure of other means to combat the disease, the previous fatal prognosis, and the low operative mortality are strong arguments in favor of splenectomy. Contraindications must be positive and adequate. Granting this, however, we must be cautioned by our imperfect knowledge of the surgical indications. The conservative selection of cases is therefore advisable.

SPLENECTOMY FOR REPEATED GASTRO-INTES-TINAL HEMORRHAGES *

DONALD C. BALFOUR

The following case is presented first to call attention to the advisability of considering the splenic factor in those cases of recurring gastro-intestinal hemorrhages in which the positive exclusion of gastric or duo-denal ulcer, the absence of both splenomegaly and a recognizable hepatic cirrhosis, contribute to a difficult diagnostic problem, and, second, because I have been unable to find in the literature any record of splenectomy performed on similar indications.

CASE (A-97,895).—C. W. E. S., a male aged forty-five, presented himself for examination in the Mayo Clinic December 30, 1913. With the exception of a tuberculous infection of the cervical glands in early life, his past history, other than that relative to his present condition, was negative.

His immediate complaint was bloody stools. From his clinical record the following facts were abstracted: For twelve or fifteen years he had been subject to epigastric discomfort one or two hours after meals, accompanied by belching of gas with sour eructations. He had noted rather indefinite food relief, but it had never been so decided that he had purposely eaten to relieve the pain. The "indigestion" was not con-stant, there being periods of complete remission, such periods being usually of a month's duration. About three months previous to his examination, after an unusually severe spell of gastric distress, tarry stools were noticed. Two or three weeks later the stools again became black, and on this occasion dyspnea on exertion, accelerated pulse, and anemia resulted. On December 13, two weeks before he came to the Clinic, a more profuse hemorrhage occurred.

The physical findings did not aid toward a clinical diagnosis. The essential reports in the special examination of the patient were as follows:

The fluoroscope demonstrated a healed tuberculosis of the apex of the right lung. The first fluoroscopic examination of the stomach was indeterminate. On second examination a possible ulcer on the posterior wall near the lesser curvative was reported. The proctoscopic report

was negative. At times the urine showed a trace of albumin, but red blood-cells and white blood-cells were always present. The gastric secretions were of normal acidity. There was a marked secondary anemia, the blood record being: Hemoglobin, 45 per cent.; red cells, 3,350,000; and white cells, 5000. The Wassermann test was negative.

A diagnosis of duodenal ulcer was made. The diagnosis was based on the chronicity and the periodicity of the "indigestion" and the bloody stools. Operation was considered urgent on account of the repeated hemorrhages and the marked anemia.

On January 13, 1914, the patient was explored. The operative findings were most unusual. The pyloric end of the stomach was markedly dilated, and enormous varicose veins were present in this portion of the stomach and along the lesser curvature. There was a distinct edema of the pancreas, which extended into the neighboring lymphatic glands. Ulcer was not demonstrated. The gallbladder, however, contained one stone impacted in the pelvis. The thickened gallbladder, the large glands, and the condition of the pancreas seemed sufficient indication for cholecystectomy. Several of the large veins on each side of the pylorus were also ligated.

The patient recovered satisfactorily from the operation and returned home. Soon after his arrival there, however, he had two copious hemorrhages from the bowel, and returned to the Clinic March 21, 1914. The hemoglobin at this time was 40 per cent., and it was thought that either a small, actively bleeding ulcer had been overlooked, or that the varicose gastric veins in some way were responsible for the bleeding. These veins were a feature of unusual interest, for such extreme varicosity in this situation is rare, and it is important to note that fatal hematemesis has occurred in which a pathologic condition other than this could not be demonstrated.

At the second operation, March 26, 1914, the pylorus was found bound down by adhesions, which were not separated. The varicose veins had become somewhat reduced in size since the former operation, and the pancreatitis was less evident. A posterior gastro-enterostomy was done on the assumption that the bleeding was due to erosions of the gastric mucous membrane.

Comparatively soon after this operation the patient began to show progressive improvement in the blood-picture, and in November, 1914, his hemoglobin and the red cells reached 84 per cent. and 4,680,000 respectively. At this time he consulted us in reference to an enlarged epididymis which was apparently tuberculous in character. December 7 a left epididymectomy with resection of the vas for tuberculous epididymis was done. His general condition was now so satisfactory that it was thought advisable to investigate the genito-urinary tract on account of the constant presence of blood-cells in the urine, the small amount of pus, and the tuberculous epididymis. Cystoscopic examination showed the left kidney to be tuberculous and the right functionating

well. On December 20, 1914, a left nephrectomy was done; the cortex of the kidney contained tuberculous abscesses.

After the nephrectomy his condition remained good until the following October (1915), when intestinal hemorrhages again occurred. There were no other symptoms except those directly incident to the bleeding. While under our observation he continued to pass black stools. On October 8, 1915, the hemoglobin was 43 per cent. Various "remedies"— tannin, coagulin, emetin—and irrigations of the stomach with hot water (130° F.) through a tube were tried, with no relief, and on October 9 the patient was again explored.

Extensive adhesions were met with through the upper abdomen. A thickening on the anterior aspect of the gastric side of the gastro-jejunal opening was found, which was looked upon at the time as an ulcer. This was excised with the Paquelin cautery and closed by suture. Very free bleeding occurred during the closure of the opening. It was hoped that this area had been responsible for the recurrence of the bleeding. The patient did well for a few days and then began to vomit bile. This was not corrected by repeated gastric lavage, and the condition finally became so critical that an entero-anastomosis between the two loops of intestine was necessary. This was combined with a jejunostomy, with a catheter to be utilized for auxiliary feeding. The patient recovered from this procedure and went home in fair condition.

He returned to the Clinic three months later (December, 1915) reporting that he had passed a quantity of dark blood on two occasions during the previous week, and for the first time had vomited a small quantity of blood the day before he returned. Examination of the blood showed the hemoglobin to be 35 per cent. He was kept under observation. The hemorrhages continued in spite of measures used to control them, and by January, 1916, the hemoglobin had dropped to 28 per cent., with about 3,000,000 red cells, and every stool examination showed blood.

The persistency of the hemorrhages and the fact that by reason of the results of splenectomy the spleen has been proved responsible for certain types of anemia associated with hemorrhages of the mucous membrane led to the consideration of splenectomy, although no enlargement of the spleen had been noted. On February 1, therefore, the patient was again explored through a left rectus incision, and the spleen, which had been questionably palpable at the costal margin previous to operation, was found to be twice normal size, its weight being 285 gm. Although the liver was not distinctively cirrhotic, an "apparently moderate cirrhosis" was noticed. Splenectomy was not particularly difficult, but as the patient was in very poor condition as a result of the repeated hemorrhages (he vomited blood on the operating table), it was of grave risk.

Recovery following removal of the spleen was necessarily slow; nevertheless it was steady, and, at the present time, seven months after the

operation, the patient is in better health than he has ever been. He weighs 200 pounds, has had no sign of bleeding since the spleen was removed, and it is confidently expected that there will be no recurrence of the hemorrhages.

The difficulty in the correct interpretation of gastro-intestinal hemorrhages is recognized by many careful observers. Preble estimates that in two-thirds of such cases a diagnosis of the cause of the hemorrhages cannot be made. In this instance the absence of an alcoholic history, with the long-standing indigestion, supported the erroneous diagnosis of duodenal ulcer. Aside from lesions of the stomach or intestinal tract, the most frequent cause of gastro-intestinal hemorrhages is splenic anemia or primary hepatic cirrhosis. Unfortunately, the clinical features and the operative findings cannot be looked upon as sufficient to make a positive diagnosis of either of these conditions. It is true, however, that the prominent symptoms in this case show a striking similarity to those which have been attributed by writers as characteristic of unrecognized or "latent cirrhosis." Preble and others have reported fatal gastro-intestinal hemorrhages associated with unsuspected cirrhosis, and Armstrong describes a case in which the necropsy disclosed no pathologic changes.

The prompt arrest of the bleeding following removal of the spleen at least suggests that the spleen, either directly, by some toxic influence, or through the medium of the liver, was responsible for the hemorrhages. The patient, who, by the way, contributed much to the satisfactory result by most intelligent coöperation, had observed that in the later months of his illness, as soon as the hemoglobin had reached about 45 per cent., intestinal hemorrhages invariably occurred, showing that even during periods of freedom from bleeding the tendency to bleed was always present.

Aside from the interest centered in the diagnostic problem, observations of distinct importance may be made. The inadvisability and the futility of gastro-enterostomy unless an ulcer can be seen or palpated have long been noted by various observers, but some cases have been reported in which "erosions" have been found at operation and in which good results have followed gastro-enterostomy. It is quite possible that in some cases of gastro-intestinal hemorrhage demonstrable erosions of the mucous membrane may be present. Armstrong reports a satisfactory result following the searing of such a surface in the gastric mucosa with

'16—40

a Paquelin cautery. These erosions are in all probability "toxic" in character.

On the other hand, the hemorrhages occurring in true cirrhosis have never, as far as I can determine, been associated with actual erosions, but have depended rather on changes in the blood-vessels and a low fibrinogen content of the blood (Whipple). This instability of the blood-vessels is shown in the tendency to petechial hemorrhages and the oozing from lips, gums, lungs, and even ears in cirrhosis. In this case, although no definite destruction of mucous membrane was demonstrated, C. H. Mayo called attention to the highly congested mucous membrane, which bled at the slightest touch. Taylor reports the case of a patient dying from a hemorrhage ten weeks following gastro-enterostomy for supposed ulcer, the necropsy revealing a marked hepatic cirrhosis.

There is an excellent illustration of the efficiency of an entero-anastomosis as a relief for bile vomiting due to an imperfectly functionating gastro-enterostomy. Most important, however, is the lesson that in every case of anemia, and particularly when the cause of the anemia is not obvious, the spleen should be considered and should be explored when an opportunity is offered. Similarly, in cases in which gastro-intestinal hemorrhages are the predominating symptoms and no ulcer can be demonstrated, the liver also should be carefully inspected and a section excised for immediate microscopic examination.

Although such gastro-intestinal hemorrhages have been usually attributed to a hepatic cirrhosis, recent developments in surgery of the spleen provide a formidable array of facts to throw considerable doubt on the assumption that the liver is the only factor in these cases. Chauffard was one of the first to point out the possibility, in some cases, that cirrhosis is secondary to processes originating, or at any rate most marked, in the spleen. The many evidences, both clinical and experimental, of the intimate relationship of spleen and liver, the excellent results following splenectomy in splenic anemia (a disease which is characterized by a tendency to develop cirrhotic changes in the liver and by gastro-intestinal hemorrhages), the fact that gastro-intestinal hemorrhage has been reported as being associated with a "latent" cirrhosis, but in which the most marked finding was a hypertrophied spleen, and last, the results of splenectomy in various blood diseases, are facts which give much prominence to the splenic factor in these obscure blood dyscrasias.

It would appear, therefore, that the result of the splenectomy herein reported opens up a wide and inviting field for investigation.

REFERENCES

Armstrong, G. E., and Mullally, E. J.: "Fatal Gastro-intestinal Hemorrhage," Amer. Jour. Med. Sci., 1914, cxlvii, 803–809.

Chauffard, A.: "Diseases of the Liver, Gallbladder, and Bile-ducts," Chicago, Macmillan, 1912, p. 188.

Preble, R. B.: "Conclusions Based on Sixty Cases of Fatal Gastro-intestinal Hemorrhage Due to Cirrhosis of the Liver," Amer. Jour. Med Sci., 1900, cxix, 263–280.

Taylor, W. J.: "A Case of Hemorrhage From the Stomach Due to Cirrhosis of the Liver in which Gastro-enterostomy was Done on the Supposition that there was Gastric or Duodenal Ulcer," Tr. Coll. Phys., Phila., 1906, 3. s., xxviii, 17–30.

Whipple, G. H.: "Hemorrhagic Disease—Septicemia, Melena Neonatorum, and Hepatic Cirrhosis," Arch. Int. Med., 1912, ix, 365–399.

A CONSIDERATION OF SOME OF THE MALADIES IN WHICH SPLENECTOMY MAY BE INDICATED *

WILLIAM J. MAYO

Physiologically, the spleen is of but moderate importance, and its removal does not cause serious changes in the human economy. The splenic vessels have only endothelial linings, and the blood comes in direct contact with the splenic pulp. The function of the spleen is obscure. From the fact that it contains non-striated muscle-fiber, which Keith,[1] in his splendid contribution to our knowledge of the nodal system, shows to be the most primitive form of control, we get an idea of its ancient heredity. We know that the cells peculiar to the spleen have phagocytic properties; that the spleen develops hemolytic ferments; that it acts as a mechanical strainer; and that it diverts a large quantity of the blood from the general to the portal circulation, for a definite purpose. The portal system of the liver has two sources: First, the gastromesenteric portal radicals, which have to do with the metabolism of food intake, and, second, the splenic portal system, which has a function perhaps somewhat similar connected with the blood. It is to be remembered that the spleen derives its blood-supply from the celiac axis, as do also those derivatives of the foregut, the liver, stomach, duodenum, and pancreas. The fact that the spleen enlarges during the digestive period and contracts in the interval is also significant. From this somewhat scanty knowledge we conclude that the spleen removes from the blood bacteria and protozoa, toxic products, and worn-out blood-corpuscles, especially erythrocytes, and sends all this material to the liver for destruction of the noxious agents and for conversion into tissue-building substances of such food elements as it may contain. While the spleen has been classified with the organs of internal secretion, there is little to substantiate the hypothesis that it possesses an important in-

ternal secretion. Organs of internal secretion are of two general types
First, those so closely associated with the sympathetic nervous system
that they act in some respects as one organ,—for example, the adrenals
and hypophysis,—and in which the internal secretions affect the tissues
largely through the sympathetics; and, second, those producing an in-
ternal secretion which is carried through the blood-stream and acts in
the body-cells directly like the thyroid secretion in metabolism (Plum-
mer,[2] Kendall[3]). It is interesting to note that most of the organs the in-
ternal secretion of which acts to a great extent through the blood-stream
were originally external secretory glands, like the thyroid, or still possess
an external as well as an internal secretion, like the pancreas, testicles, etc.

Pathologically, the spleen is of very great importance. It is a link in
a chain of organs which, under conditions of disease, produces changes
in the blood that may eventually cause death. However, the spleen
constitutes only a single weak link in the chain—a link which may be
removed. In many instances its removal breaks up a vicious circle and
the patient is thus restored to health, even though the spleen itself may
be only the agent of destruction rather than its cause. This conception
of the function of the spleen brings into the foreground its relation to
the pathology of the blood as a tissue—a tissue composed of leukocytes,
erythrocytes, and platelets, the plasma of the blood having the relation
of connective tissue.

One hundred and thirty-five splenectomies have been performed in
our Clinic for various conditions. There were 12 deaths—a mortality of
8.5 per cent. This takes into account all deaths that occurred in the
hospital after splenectomy, without regard to their cause or the length
of time they occurred after operation. This method of computation
works some hardships, but it seems to be necessary, in order that our
statistical values may have a common basis. While the function and
pathology of the spleen are more or less obscure, the outstanding fact
in these cases was that, with one exception, the spleen was enlarged and
the enlargement concerned those pathologic states with which it was
associated.

The enlargement of the spleen may at times be a work-hypertrophy,
such as occurs in hemolytic jaundice. In other cases, as in pernicious
anemia, the spleen may have been stimulated to pernicious activity. In
splenic anemia the blood destruction originates perhaps within the spleen
itself, as a result of those agents which cause the enormous growth of
fibrous tissue in the spleen and the terminal cirrhotic process in the liver.

As the blood-picture is not characteristic, the estimation of the relation of the spleen to these various disorders depends largely on our ability to ascertain the physical condition of the spleen. Unless the spleen is enlarged, we have at present no evidences which necessarily denote splenic disease.

A somewhat careful investigation as to the value of percussion in detecting enlargement of the spleen not sufficiently marked to be discovered by palpation does not give percussion as high a place as we have been led to believe it held. On many occasions I have carefully mapped out what I concluded to be the area of splenic dulness by percussion, and on opening the abdomen found I had been greatly deceived. Much of the belief in the accuracy of outlining the spleen by percussion has been due to the fact that this method was employed in such diseases as typhoid and malaria, in which enlargement of the spleen was found after death. In the large majority of cases little real knowledge of the physical condition of the spleen will be obtained unless it can be felt by careful palpation on full inspiration, with the patient lying on the right side. This is unfortunate, as the spleen must be enlarged several times its normal size to become palpable. Carman is now developing roentgenologic evidence as to splenic enlargement which it is hoped will produce reliable information.

For convenience, the diseases with which the spleen is concerned may be roughly classified into three groups: (1) Splenomegalias of parasitic origin; (2) splenomegalias of probably toxic origin, associated with anemia and cirrhosis of the liver; and (3) splenomegalias associated with blood dyscrasias.

Splenomegalias of Parasitic Origin.—Under normal conditions parasitic agents collected in the spleen are sent to the liver for destruction, the spleen appearing to have little germicidal power. Should parasites accumulate beyond the ability of the spleen to rid itself of them, such secondary conditions occur as are shown in the splenomegalias of typhoid, malaria, syphilis, tuberculosis, and other infections. Eventually such cases may come to operation because of the failure of medication to reach the organisms sequestered in the spleen, which have a constant tendency to reinfect the whole body.

A study of the sequestration of parasites in the spleen has many interesting features. We must believe that a certain number of bacteria gain entrance to the blood, but that in health they are eliminated in various ways, many being removed from the blood-stream in the spleen

and destroyed in the liver. Adami[4] has shown that bacteria are constantly picked up in the duodenum and upper jejunum and sent to the liver for destruction, and that the pigmented areas frequently seen in the liver at postmortem are the result of collected pigment from slaughtered bacteria. Bacteria in the blood are derived from various sources. Eccles,[5] in commenting on the power of the body-cells to resist bacterial invasion, calls attention to the fact that such resistance is a response to the action of bacteria that are early introduced into the blood-stream, and that an early introduction of bacteria, such as occurs in some instances through the tonsils, is essential to the development of this defense. If this is true, the tonsils and kindred organs may on occasion assume the rôle of immunizers, permitting just a sufficient number of bacteria to enter the circulation at an early stage of the infection to develop resistance to the specific organism. Vaughan[6] points out that typhoid infection of the body is present during the prodromal period, and that what we call typhoid fever is the defense manifestation set up as the result of this infection, the period of incubation being the time necessary to educate the body-cells to resist the typhoid bacillus. From this standpoint it may be said that bacteria circulating in the blood at times have a definite value. Must we believe that all the blood of the body passes through the spleen in a haphazard manner in order to strain out the bacteria, or does the spleen have a definite attraction for certain types of bacteria? Rosenow's[7] extraordinary work showing the specificity of bacterial infection would lead us to believe that the spleen specifically attracts to it, from the blood-stream, the various bacteria and toxic agents which it is its function to gather up for elimination.

While we have seen a number of cases of typhoid splenomegalias and operated on several typhoid abscesses of the spleen, none has required splenectomy. We have not seen a case of the ague-cake of malarial plasmodium requiring operation, although Jonnesco[8] has reported a number of splenectomies for this condition in which the operation was necessary because of inability to destroy the plasmodium in the spleen and relieve the chronic cachexia and anemia by medication. Jonnesco's mortality was high, but the patients who recovered from the operation were cured.

We have had but one case of probable primary tuberculosis of the spleen—that of a young girl in whom there was no other evidence of tuberculosis at the time of the operation, but who died of generalized tuberculosis within six months. We must believe it possible, therefore,

that the splenic condition was but the dominant feature of an unrecognized dissemination of tubercle bacilli.

Four patients have been splenectomized for syphilitic splenomegalia. Three had definite histories of lues, all had positive Wassermanns, and spirochetes were found in the removed spleens in two cases. Two spleens contained a few small, typical gummas. In three cases gummas were found in the liver. The patients were markedly anemic and had failed to improve satisfactorily under salvarsan, neosalvarsan, and prolonged mercurial treatment. Removal of the spleen was followed immediately by an extraordinary improvement in the anemia. After operation the patients were again placed on antispecific medication, and their recovery was prompt and permanent.

For splenomegalias of pyogenic origin we have removed the spleen nine times, with one death. These cases will be reported in detail later.

Splenomegalias of Toxic Origin Associated with Anemia and Cirrhosis of the Liver.—The splenomegalias in this group were due evidently to toxic products which had been removed from the blood, and which, passing to the liver, evidently produced hepatic cirrhosis. We infer that such toxins are filtered out in the spleen, and we know that in certain diseases removal of the spleen not only cures the anemia, but tends also to check the progress of the cirrhotic process in the liver, such as occurs in Banti's disease.

It appears that nature has several methods of destroying toxic agents, among them being absorption, elimination, and encapsulation. It may be that the latter of these processes is active in cirrhosis of the liver. The spleen collects from the blood and distributes through the radicles of the portal vein certain toxic products which, for a time, in the earlier stages of the disease, the liver is able to destroy and eliminate. When it fails in this elimination the diffused poisons are encapsulated, this diffuse encapsulation resulting in portal cirrhosis. It is probable that most toxic agents which act as causes of portal cirrhosis, alcohol, for example, are derived through the mesenteric portal system, but sufficient evidence is now at hand to show that the same process may be set up by agents derived from the spleen, and that the occurrence of splenomegalia in connection with portal cirrhosis may indicate a relationship between the splenomegalia and the causation of the cirrhosis. Another view in regard to the splenomegalia is that it is compensatory to the hepatic failure, but as the removal of the enlarged spleen in the recorded cases appears to have done no harm in any of the types of hepatic cirrhosis, and often

resulted in great good, the former hypothesis appears the more reasonable.

Clinically, splenic anemia is the best understood member of this group, but it rests on an insecure pathologic basis. There are many varieties. An enlarged spleen and the secondary type of anemia, however, are more or less characteristic, although the anemia may be absent for long intervals.

Gaucher's disease is usually included in the splenic anemia group. Brill and Mandelbaum,[9] however, point out that it could be classified more naturally with new-growths, as it is essentially a disease of endothelial characteristics. Herzog [10] points out that the anemia which results from Gaucher's disease is characteristic of splenic anemia, but admits that after death from Gaucher's disease the peculiar endotheliomatous growths are found in the liver and other organs. When the spleen was removed before these terminal changes appeared the patients were cured, as occurred in cases cited by Herzog and also in our experience. Gaucher's disease usually begins before the thirteenth year, and runs a chronic course, often lasting twenty-five years or more.

Von Jaksch's disease, anæmia pseudoleukæmica infantum, according to Giffin,[11] is probably best classified with splenic anemia, the high white-cell count and lymphocytosis being due to a peculiar reaction of the infant's blood. While the milder types of von Jaksch's disease are usually cured by general treatment, splenectomy is required for the more severe types.

There is less evidence to indicate that a splenomegalia peculiar to it may be a cause of biliary cirrhosis, but the results in the few cases of splenectomy we have performed in cases of biliary cirrhosis have led us to believe that to a certain degree it has a definite relation to the hepatic condition, and that the latter may be favorably modified, at least in some cases, by the removal of the spleen.

In splenic anemia the spleen is enlarged, and thus its power of destroying red cells is increased, as is shown by the increase of hematin and the relative increase of leukocytes in the splenic vein. There is also a great increase of connective tissue in the spleen, which may be the result of some toxic stimulant. Secondary cirrhosis of the liver, which completes the syndrome of splenomegalia and anemia, as described by Banti, represents a late stage of the process. In all we have done 43 splenectomies for splenic and allied anemias (Gaucher, von Jaksch's disease, etc.). Five of the patients died. The mortality in this group was too

high, and represents badly chosen cases in our earlier experience; it can be readily reduced to 5 per cent. The improvement that takes place on removal of the spleen in successful cases is surprising. Even in late stages of the condition in which there is marked cirrhosis of the liver the patients may be apparently cured. It would seem that the great power of the liver in regenerating its specific cells must be utilized to the full extent to produce the improvement which occurs after splenectomy for advanced Banti's disease.

In several of our cases of splenectomy for splenic anemia in which there was marked splenomegalia with advanced cirrhosis of the liver and ascites the patients were restored to health—in one instance now for more than seven years. One of the typical features of splenic anemia is the occurrence of hemorrhages from the stomach. Possibly 75 per cent. of all the severe hemorrhages from the stomach do not have their origin, as is so frequently thought, in peptic ulcer, but arise from some unknown gastrotoxic condition. They occur more often in adult males. Usually there are no previous symptoms, gastric or otherwise, and after recovering from the hemorrhage, which may have been very severe, the patient becomes symptomatically well. These hemorrhages markedly resemble those which occur in splenic anemia. Some authorities believe they are the result of unrecognized cirrhosis of the liver, though not necessarily of the rupture of enlarged veins. In several cases of gastric hemorrhage in which we explored the stomach during the period of bleeding widespread superficial changes in the gastric mucosa, but no peptic ulcers, were found. Armstrong[12] has reported similar cases in which he was able to check the hemorrhage by passing a hot iron over the bleeding surfaces. In none of the reported cases, however, was the condition of the spleen mentioned. In a very remarkable instance of this kind in which the patient had had a number of operations for gastric hemorrhage, with recurrence of the hemorrhage whenever the hemoglobin rose above 45 per cent., Balfour[13] explored the spleen and found that it was more than twice the normal size. In the liver were some slight changes which might be regarded as a possible early cirrhosis. The spleen was removed; the man gained 60 pounds in weight; his hemoglobin rose above 80 per cent., and he has been in perfect health for one year. In Balfour's opinion many cases of hemorrhage from the stomach of unknown causation may be of splenic origin, and he suggests that in all operations for gastric hemorrhage the condition of the spleen be noted, since in this way valuable data may be accumulated. It is quite possible that up to the present

time we have been recognizing as splenic anemias only those gross conditions which may be the terminal stages of a more frequent malady.

The resemblance between splenic anemia with terminal portal cirrhosis of the liver and those cases of portal cirrhosis in which the enlargement of the spleen is apparently secondary to the cirrhosis has led us to remove the spleen in three selected cases of advanced portal cirrhosis with splenomegalia, ascites, etc. In one instance it was impossible to tell, from the history or physical examination of the patient, whether the portal cirrhosis was primary and the splenomegalia secondary or the reverse. The operations are too recent for any conclusions, but the patients who recovered showed a remarkable improvement of the anemia and a lessening or disappearance of the ascites, and from a wholly incapacitated state are now in fair health. In three instances we removed an enlarged spleen associated with biliary cirrhosis. These persons were moderately jaundiced and had large livers and spleens. Their condition has been very greatly improved, and they have been able to return to work, though two still have slight jaundice. One is apparently cured. One of these cases may have been confused with Hanot's cirrhosis, if there be such a pathologic entity.

Splenomegalias Associated with Blood Dyscrasias.—In fetal life the spleen, the bone-marrow, the lymphoid and adenoid structures of the body, and probably the liver, are concerned in the formation of blood. The most primitive blood is white blood, the white cells descending from the mesenchyme cells and the red cells derived from the white cells. All animals having but one kind of blood have white blood. The earliest fetal blood is white. Leukemia has been regarded as a cancer of the white blood tissue—an uncalled-for, functionless production of embryonic cells in which all the original blood-forming organs take part, just as sarcoma concerns embryonic connective-tissue cells and carcinoma concerns embryonic epithelial cells. Leukemia varies greatly according to the particular group of organs in which the diseased blood production is most marked. However, clinical evidence that cannot be ignored has been brought out recently which at least leads to the conjecture that leukemia may be more definitely connected with certain organs than we have been led to believe. In splenomyelogenous leukemia, for instance, the application of the x-ray over the spleen at first acts most beneficially in reducing its size, decreasing the white cells, and improving the anemia, but later the ray loses such power. Radium applied at several points over the spleen has a much more rapid effect than the x-ray. In several cases

in our experience applications of radium caused so great a reduction in a huge spleen within a month that it could not be felt beyond the margin of the rib. Coincidentally the white cells dropped from several hundred thousand to less than 10,000. Our experience with the x-ray in the treatment of splenomyelogenous leukemia does not indicate that these spleens so markedly acted on by radium will remain permanently in abeyance. It is to be noted that after the improvement produced by the x-ray ceases enlargement of the spleen again takes place coincidentally with the increase in the white cells. This leads to the question as to whether or not, during the period of abeyance, splenectomy might not have had a further effect in extending the palliation in certain types of disease allied to splenic leukemia.

An experience with a case recently is at least suggestive:

CASE A171,009.—A woman, aged fifty-six years, suffering from splenomyelogenous leukemia with the usual blood-picture, was admitted to the Clinic for examination September 15, 1916. White blood-cells, 203,000. The spleen filled the left half of the abdomen. Over the splenic area was an x-ray dermatitis. The history developed the fact that at first x-ray treatment had been of much benefit. The spleen was markedly reduced in size, and there was a great reduction in the number of white cells and improvement in the patient's general condition. Later the x-ray lost its effect; the spleen rapidly increased in size, the leukocyte count went up, and the patient's general condition went down. The spleen, weighing 1100 gm., was removed. The outer portion of the organ was somewhat sclerosed, evidently the result of the treatment. Possibly this outer sclerosis prevented further effect from the x-ray on the hyperplastic splenic pulp sequestered in the middle of the organ. The leukocytes dropped from 203,000 to under 50,000 in the first ten days after the operation. We must anticipate that this patient will eventually die with leukemia. A study of the future course of the disease will be interesting.

Several patients in our experience in whom the spleens were large and the white blood-cells up to 30,000, and who had been diagnosed and treated as leukemic, were cured by splenectomy. I do not wish to be understood as recommending splenectomy as a cure for leukemia, but it seems consistent, especially when we remember our fogginess of mind in regard to the early leukemic state, that in selected cases of this type splenectomy may be considered after the application of radium and during the period of great improvement.

Pernicious anemia has been pictorially spoken of as a cancer of the

red-cell tissue. Postmortem examinations have usually shown that the spleen is not enlarged after death from pernicious anemia; that, if anything, it is atrophic. Therefore it has been assumed that the organ does not have anything to do with pernicious anemia, although in many reported cases it was distinctly enlarged. In the cases in which we have removed the spleen for pernicious anemia it was found enlarged from two to ten times its normal size, with one exception. In this case the patient was in a terminal condition, and the spleen was slightly atrophic (187 gm.; normal, 195 gm., Sappey). This suggests that the shrunken spleen found at postmortem is a terminal condition.

Previous to the time of Eppinger's[14] reports the spleen was removed in a number of instances of pernicious anemia under a mistaken diagnosis. In one of our patients in whom the spleen was large, the anemia marked, and the blood lacking in pernicious cell characteristics, the spleen was removed under the impression that the disease was splenic anemia. This patient lived in fair health for three years and died from an intercurrent malady. Before death the condition was proved to be pernicious anemia by the development of a typical blood-picture.

That pernicious anemia in any great percentage of cases depends entirely on splenic disease I do not believe can be held, but clinical experience has proved that the spleen may be a factor of considerable importance. The removal of the spleen in suitable cases after the failure of other therapy has given rise to prolonged betterment, but splenectomy does not seem to prevent the development of cord changes nor do the pernicious cells entirely disappear from the blood. Eppinger believes that these manifestations are terminal, and that if the spleen is removed sufficiently early, they will not appear. The time of observation is as yet too short to warrant speaking with any degree of authority as to what the ultimate possibilities of splenectomy in the therapeusis of pernicious anemia may be. It has been said that if the spleen is the mother of pernicious anemia, there must be many fathers.

In 48 cases of pernicious anemia in which we removed the spleen there were 3 deaths. I am convinced that the deaths were unnecessary, as none occurred in the last 29 operations. The patients who died were in an advanced stage of the disease, and were operated on during crises without transfusion. In the operations performed when the patients were on the upgrade, or when we were able to start the upgrade by transfusion, there were no deaths. Miller[15] says that the removal of the spleen

may act either by stimulating the bone-marrow or by increasing the resistance of the erythrocytes.

To Giffin, who has paid most careful attention to these cases, the writer is indebted for the following summary of the indications for splenectomy in pernicious anemia:

"There is no evidence that splenectomy has cured pernicious anemia. A review of 48 cases of splenectomy for pernicious anemia demonstrates a definite gain in the blood, the weight, and the general condition during the first three months of the postoperative period in 78 per cent. of the cases; during the second three months' period, 68 per cent. of the living patients maintained their gain. A consideration of the advisability of splenectomy would seem to be warranted at present chiefly in young and middle-aged patients of good general resistance, who show evidence of active hemolysis and in whom the spleen is moderately enlarged. The estimation of the blood-derived pigments in the duodenal contents is valuable in determining the degree of hemolytic activity present at a given time. A comparison of the degree of hemolysis with the severity of the anemia would seem to be indicative of the productive power of the bone-marrow. Preoperative treatment, especially transfusions, should be employed to influence the patient's general condition and to improve the characteristics of the blood-picture. The operative risk is increased when the hemoglobin is below 35 per cent. and the erythrocyte count less than 1,500,000. Postoperative transfusions have not been given as a routine procedure, but transfusions have been successfully employed in postoperative relapse."

Hemolytic jaundice presents a brighter picture than pernicious anemia, and with splenic anemia represents the triumph of splenectomy. It would appear that the function of breaking down worn-out corpuscles is exercised by the spleen in response to some condition of the red corpuscle itself. It has been shown that the cells peculiar to the spleen have phagocytic properties, but in most careful investigation Herzog was never able to find red cells engulfed by splenic cells. The ferment theory, therefore, appears to fit the conditions best, although it is a question whether such ferments are produced in the spleen or carried to the spleen to produce their effect. Chauffard and Widal[16] have shown that in hemolytic jaundice the red corpuscles are more fragile than normal as they circulate in the blood, and their fragility is apparently their death-warrant in the spleen. Some organ or tissue in the body places the death sign on the red corpuscles and the spleen obeys the command.

The hypertrophy of the spleen under these circumstances is possibly to be looked upon as a work-hypertrophy. Certain it is that the removal of the spleen in hemolytic jaundice institutes most marvelous improvement and speedy cure. The jaundice, which may have existed for years or possibly for life, entirely disappears within a few days, and the anemia, which is of the secondary type, disappears within two or three weeks.

Hemolytic jaundice is of two types—the acquired type of Hayem and Widal, and the familial or congenital type of Minkowski. The former is the more serious and usually leads to death. The latter may exist for years or for a lifetime, the patients maintaining a fair degree of health, although suffering at times from an exacerbation of slight permanent jaundice, accompanied by tenderness in the region of the enlarged liver and spleen, headaches, malaise, and moderately increased temperature. The acquired type of hemolytic jaundice has probably been confused with biliary cirrhosis, and there are reasons to believe that many patients supposed to be suffering from the hypertrophic cirrhosis of Hanot, a disease lasting from six to ten years, and most frequent in the adolescent period, in reality have hemolytic jaundice. The enlarged spleen and liver of hemolytic jaundice lend themselves readily to such confusion. This confusion should no longer exist unless there are gallstone complications, for in hemolytic jaundice bile is found freely in the stool but not in the urine. Examination of the peripheral blood discloses an increased fragility of the red cells, and Schneider's[17] test of the duodenal contents removed through the duodenal tube shows urobilinogen and urobilin in excess. Unfortunately, however, gall-stones are very frequently present, perhaps because of an increased viscidity of the bile, and may give rise to colics, cholangitis, biliary obstruction, etc.

The choice of time for splenectomy in hemolytic jaundice is of importance. Of 13 cases, we lost but one, this being a patient who was operated on during crisis. For our knowledge of hemolytic jaundice we are greatly indebted to the work of Elliott and Kanavel.[18]

To sum up, it may be said that splenectomy is a curative measure in properly selected cases of splenic anemia, hemolytic jaundice, and allied states, and that it may be curative in certain as yet little understood conditions which are confused with pernicious anemia, leukemia, and cirrhosis of the liver. Splenectomy is of value in certain types of parasitic splenomegalia, notably malaria and syphilis. It is of value for the palliation of some types of pernicious anemia. In portal and biliary cirrhosis associated with splenomegalia splenectomy may have a field of

usefulness, but there has not been sufficient experience with it in these conditions to furnish reliable data. In true leukemia splenectomy does not appear to have standing, but in connection with the use of radium it is at least to be considered.

The technic employed in the Clinic for splenectomy has been recently described by Balfour,[19] and it will not be necessary to lengthen this discussion by further reference to it.

In conclusion, I wish to emphasize the fact that traditional medicine has named many diseases from symptom-complexes. Patients are more or less carefully observed, a few blood-cells and a little plasma are examined at various times, the patients die, and we assume that the condition found after death existed during life. The history of medicine is a graveyard of such beliefs. The spleen is one of the latest of the hidden organs to be brought under the eye and investigated during life and in the early stages of disease. We find that the problems presented are not simple, but rather very complex. In the early stages splenic anemia may be confused with pernicious anemia, cirrhosis of the liver, hemolytic jaundice, and leukemia. We remove the spleen and say we have cured any one of the diseases we may have fixed upon to designate the condition, but does that make it true? Where is the dividing-line between hemolytic jaundice, Hanot's cirrhosis of the liver, and some types of pernicious anemia? In the terminal stages we recognize the name of the end-results, but to determine the nature of the disease in the early and curable period requires investigation of the spleen, liver, bone-marrow, and blood during life. To do this judicially we must divest ourselves of accumulated prejudices which are the result of a nomenclature based on symptoms.

REFERENCES

1. Keith, A.: "A New Theory of the Causation of Enterostasis," Cavendish Lecture, Lancet, 1915, ii, 371–375.
2. Plummer, H. S.: "The Function of the Thyroid, Normal and Abnormal," Tr. Assoc. Amer. Physicians, 1916.
3. Kendall, E. C.: "Studies of the Active Constituent, in Crystalline Form, of the Thyroid," Tr. Assoc. Amer. Phys., 1916.
4. Adami, J. G.: "On Latent Infection and Subinfection and on the Etiology of Hemachromatosis and Pernicious Anemia," Jour. Amer. Med. Assoc., 1899, xxxiii, 1509–1514, 1572–1576.
5. Eccles, R. G.: "The Tonsils and the Struggle for Existence," Med. Rec., 1915, lxxxviii, 47–56.
6. Vaughan, V. C.: "Infection and Immunity," Commemoration volume, Chicago, Amer. Med. Assoc., 1915, p. 164.
7. Rosenow, E. C.: "Elective Localization of Streptococci," Jour. Amer. Med. Assoc., 1915, lxv, 1687–1691.
   "Elective Localization of Bacteria in Diseases of the Nervous System," Jour. Amer. Med. Assoc., 1916, lxvii, 662–665.

8. Jonnesco, T.: "Splénectomie pour hypertrophie malarique," Bull. et mém. Soc. de chir. de Bucarest, 1901-2, iv, 58.

9. Brill, N. E., and Mandelbaum, F. S.: "Large-cell Splenomegaly (Gaucher's Disease): A Clinical and Pathological Study," Amer. Jour. Med. Sci., 1913, cxlvi, 863–883.

10. Harris, M. L., and Herzog, M.: "Splenectomy in Splenic Anemia or Primary Spleno-megaly," Ann. Surg., 1901, xxxiv, 111–134.

11. Giffin, H. Z.: "Splenectomy for Splenic Anæmia in Childhood and for the Splenic Anæmia of Infancy," Ann. Surg., 1915, lxii, 679–687.

12. Armstrong, G. E.: Personal communication.

13. Balfour, D. C.: "Splenectomy for Repeated Gastro-intestinal Hemorrhages," Ann. Surg., 1917, lxv, 89–94.

14. Eppinger, H.: "Zur Pathologie der Milzfunktion," Berl. klin. Wchnschr., 1913, l, 1509–1512, 1572–1576, 2409–2411.

15. Miller, J. L.: "Splenectomy in Splenic Anemia, Hemolytic Icterus and Hanot's Cirrhosis," Jour. Amer. Med. Assoc., 1916, lxvii, 727–730.

16. Chauffard, A.: "Pathogénie de l'ictère congénital de l'adulte," Sêm. méd., 1907, xxvii, 25–29. "Les ictères hémolytiques," ibid., 1908, xxviii, 49–52. "Cholélithiase pig-mentaire dans un cas d'ictère congénital hémolytique; analyse chemique des cal-culs," Bull. et mém. Soc. méd. d. hôp. de Paris, 1912, xxxiv, 80. Widal, F., Abrami, P., and Brulé, M.: "Différenciation de plusieurs types d'ictères hémolytiques," Presse méd., 1907, xv, 641–644. Cited by Elliott and Kanavel, loc. cit.

17. Schneider, J. P.: "The Splenic Pathology of Pernicious Anemia and Allied Conditions," Arch. Int. Med., 1916, xvii, 32–41.

18. Elliott, C. A., and Kanavel, A. B.: "Splenectomy for Hemolytic Icterus," Surg., Gynec. and Obst., 1915, xxi, 21–37.

19. Balfour, D. C.: "Technic of Splenectomy," Surg., Gynec. and Obst., 1916, xxiii, 1–6.

BLOOD

CHRONIC HEART BLOCK *

JOHN M. BLACKFORD AND FRED A. WILLIUS

We have had an opportunity to observe nine cases of chronic heart block during the past two and one-half years. The effect of therapeutics in the last four cases seems worthy of presentation at this time, because we have been administering a drug not hitherto mentioned in cardiac treatment and have been apparently successful in increasing the idio-ventricular rate, with marked relief of symptoms.

Complete chronic heart block is now recognized to be due in all cases to a functionally complete break in the auriculoventricular bundle. This failure of conduction is proved to be due to organic severance of the bundle in the great majority of all carefully autopsied cases, and we may assume that the few exceptions are failures in present methods of objective study rather than actual exceptions.

The pathology of chronic heart block is too well known to justify elaboration. Inflammation and degeneration of the bundle, infiltrating gummas and neoplasms involving the bundle, are the chief lesions described. Valvular disease or coronary sclerosis is usually present. Mitral disease is the most frequent valvular lesion.

The changes in cardiac rhythm, progressing from a definite prolongation of the auriculoventricular interval to the dropped beat, then to the 2-1 and 3-1 rhythm, and finally to complete dissociation of rhythm, are now fully recognized. The Stokes-Adams syndrome results from circulatory changes which produce cerebral anemia, i. e., the syndrome may manifestly be due either to temporary stopping of the ventricles, or in certain cases to little runs of rapid contractions which are inefficient in their pumping action. In certain cases the syndrome is brought on by exercise, since there is no compensatory increase in the ventricular rate. Cases have been reported in which complete block has existed for many years with little or no discomfort to the patient, and in which no other

organic lesion was evident. However, such cases, as we have seen them, are the small minority. Most patients with chronic heart block are confirmed cardiopaths and subject to the Stokes-Adams syndrome, with its attendant dangers.

We know that the vagus gives branches to the sinus node, to the auriculoventricular bundle, and that stimulation causes slowing of the heart by inhibition of the sinus and of the conducting bundle. The cardiac accelerator nerves have a similar distribution, but they act to increase the sinus rate. So far as has been proved, they cause no increase of the idioventricular rate. Digitalis is recognized as stimulating the vagus and thus slowing conduction in the bundle, though therapeutic doses often produce no rate reduction in a sinus rhythm or tachycardia. No drug or measure is known which increases the idioventricular rhythm; yet such result is manifestly desirable in chronic heart block.

Thyroid extract will excite a tachycardia in the normal organism. Such effect is produced probably by action on the accelerators or a direct stimulation of the sinus node, though no experimental work is available to prove this action. A large mass of clinical evidence without laboratory proof shows that thyroid extract markedly affects the myocardium, as illustrated by the irritable and rapid action, with concomitant myocardial degeneration of the thyrotoxic heart.

During the examination of a case of chronic heart block we thought of attempting to increase the idioventricular rate by the administration of large doses of alpha-iodin, the active constituent of the thyroid which Kendall has isolated recently. The administration of this drug has been followed in four cases by marked improvement in the patients' nutrition, associated with increased ventricular rate and cessation of the Stokes-Adams syndrome, though one patient has since died. The histories of these four patients are briefly as follows:

CASE 1 (134,644).—Male, aged forty-two years. No history of rheumatism, tonsillitis, chorea, or lues. Following diphtheria at twenty years, he suffered from occasional palpitation and rapid heart action for a short time, but made a complete recovery. A slow pulse was noted at times for eight or ten years, but he was considered healthy until two and one-half years before coming to the Clinic, when, during an attack of measles, his doctor found his pulse 42. The pulse had been slow ever since, averaging 37 and never being faster than 40. The patient suffered from occasional spells of "palpitation." He had gradually become dyspneic and unable to work, but had never been in bed. Two weeks previously he began having "sinking spells"; suddenly became dizzy and

his heart seemed to stop. He was momentarily unconscious, without convulsions and with instant recovery. Any exertion brought on a spell. During the previous few weeks he had 10 to 12 such spells a day.
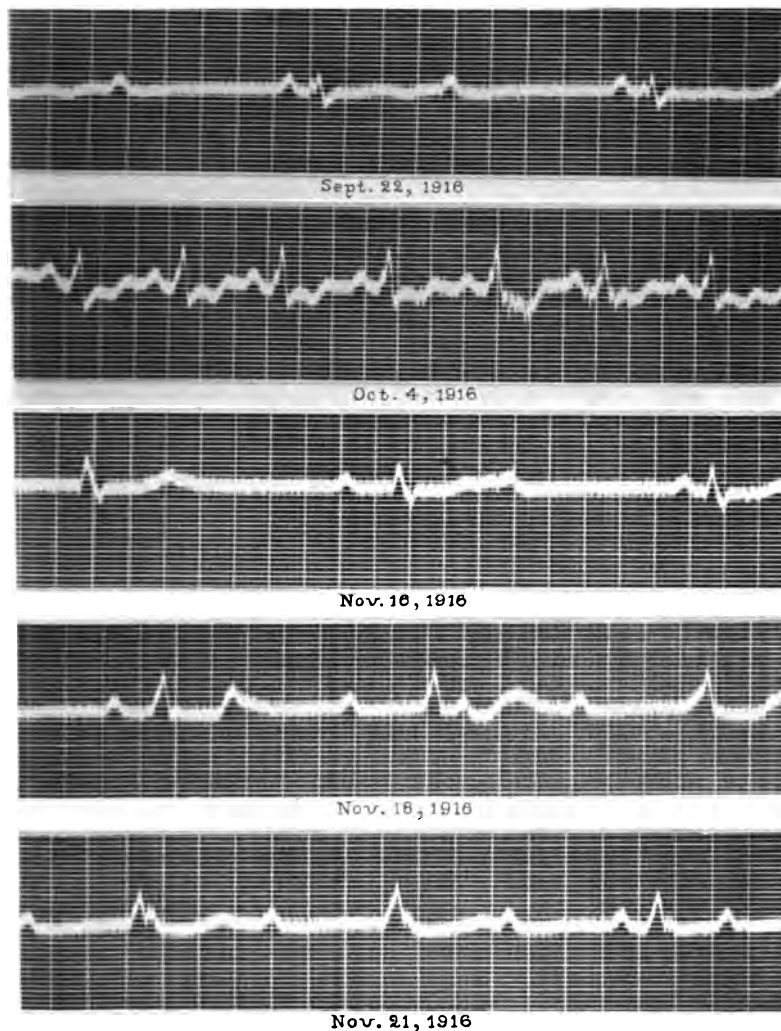
Fig. 291.—(Case 173,079.) Lead II showing: (1) Ventricles 32 with complete dissociation; (2) sinus rhythm reëstablished after alpha-iodin; (3) complete dissociation reëstablished after medication was discontinued; ventricular rate, 33; (4) ventricular rate increased to 40 under alpha-iodin; and (5) ventricular rate 43 under treatment.

Physical Examination.—Blood-pressure, 112-60. Pulse, 36. Heart 6 inches to the left and a very loud harsh systolic mitral murmur with heaving apical impulse.

Diagnosis.—Bradycardia with mitral lesion, probably double, and myocardial insufficiency. Electrocardiogram showed complete dissociation, with auricles 71, ventricles 36. Wassermann negative. The administration of $\frac{1}{30}$ grain of atropin by mouth caused no change in the action of the heart.

Treatment.—The patient was put on alpha-iodin, 3 mgm. daily, with
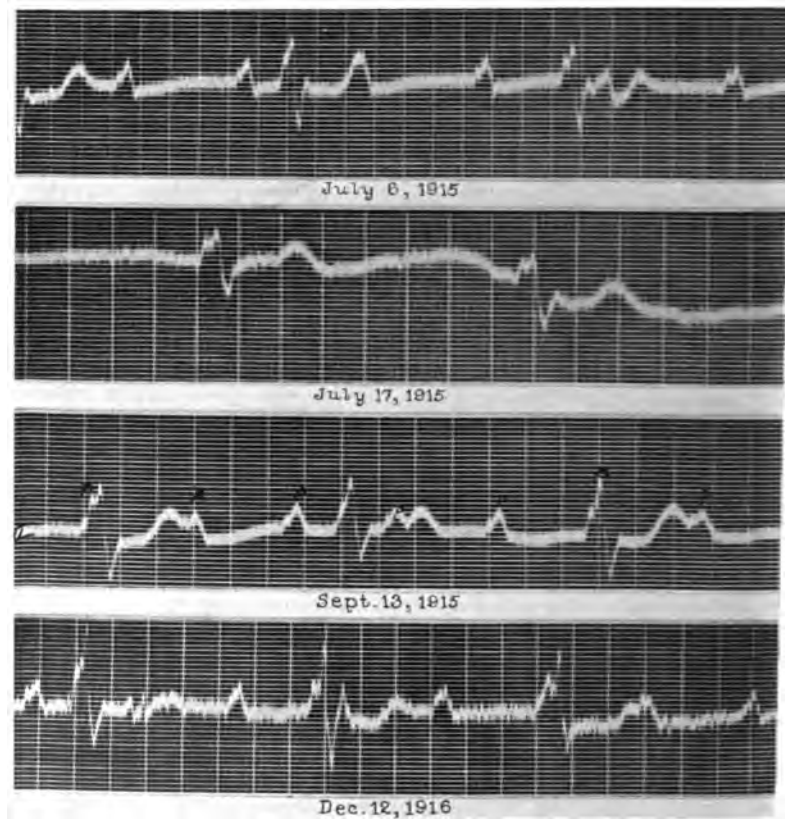
Fig. 292.—(Case 134,644.) Lead II: Complete dissociation. (1) Auricles 75, ventricles 32. Alpha iodin administration begun. (2) Auricles 83, ventricles 40. (3) Auricles 106, ventricles 106. (4) Auricles 105, ventricles 45.

prompt rise in auricular rate in five days to 88. On the tenth day the ventricular rate increased to 40. The spells disappeared after several days of treatment. For eleven months there were no spells, and the pulse was 40 to 48 constantly. During this time he came to the Clinic five times for observation. The medicine then gave out; he had no treatment for a few days, and the spells (very violent) promptly returned. The pulse slowed to 32, and he came back for observation and treatment.

When coming to the Clinic he fell on the street and cut his head. During the first few days 3 mgm. of alpha-iodin were given daily, and as before, there were repeated hard spells with many little ones. After two weeks of treatment he was dismissed to continue medication at home. Five months later he reported that he was doing light farm work and had had no further spells. His ventricles now average 48 and auricles 105.

This patient was relieved of symptoms during sixteen months without relief of the block. The idioventricular rate increased, with marked improvement in general nutrition and a gain of 15 pounds in weight. His improvement apparently depends on continued medication, evidenced by prompt return of the syndrome when medication is stopped.

CASE 2 (173,079).—Male, aged sixty-four years. No tonsillitis or rheumatism. Denied venereal infection. He had had grip twenty years previously, and following this, dyspnea and at times pounding of the heart, but he entirely recovered. Three years previously he began to be dizzy, and was treated for heart trouble. Edema of the legs was noted two years later. Recently he had two fainting spells, possibly apoplectic. He had known of a very slow pulse for at least four months, and during this time exertion had caused "dizzy spells" lasting a few seconds. He immediately stopped exertion until he felt well again.

Physical Examination.—Heart 5 inches to the left and 1 inch to the right; rate, 30; loud systolic blow at apex. Eye-grounds showed arteriosclerotic vessels and rather hazy discs. The brachials were very sclerotic. Electrocardiogram showed complete block, with auricles 66, ventricles 32. Wassermann negative.

Treatment.—Digitalis, 20 drops three times a day, and alpha-iodin 2 mgm., was begun September 25, 1916. On September 28 sinus rhythm (rate 90) was restored, but with marked evidence of impaired intraventricular conduction, as evidenced by the wide-spread R wave. Medication was discontinued on October 5, and during one week of observation the sinus rhythm was maintained. The patient went home for a month, then returned with his block reëstablished for one week. He was again placed on the same treatment, and his ventricular rate increased from 32 to 44 in a few days. He again asked to go home for a day, and the next morning, at his home, dropped dead. Permission for necropsy was not obtained.

It is evident that in this case the block was functionally but not anatomically complete. The increased irritability produced by the alpha-iodin appears to have relieved the functional block by increasing the irritability of the junctional tissues along with the myocardium. After medication was stopped the relief continued for four weeks, with marked subjective improvement. The block recurred, however, and the patient died suddenly twenty-two days later in spite of the fact that his ventricular pulse was again responding to the treatment.

CASE 3 (145,901).—Male, aged sixty-one years. Neisserian infec-

tion twenty-five years previously and lues questionable. Wassermann negative. He complained of stiffness of the spine and dizziness on exertion. The cardiac history was of four to six years' duration. He had attacks of "all-gone feeling" extending from stomach to neck, and momentary dizziness. Such attacks usually followed exertion, but occasionally came on at other times.

Physical Examination.—General condition fair. Pulse, 36 to 40. Heart 4½ inches to the left, with loud systolic blow over whole pericardium. There were a very marked spondylitis deformans and a large right branched kidney stone. The dental rays were negative. Electrocardiogram showed complete block, with auricles 107, ventricles 41.

Treatment.—Operation for the kidney stone was obviously not indicated. After observation in the hospital for five days, during which time the pulse averaged 41, with 32 and 50 as extremes, the patient was given alpha-iodin, 3 mg. daily. On account of nervous symptoms this amount was dropped to 1 mg. on the seventh day, and the observation continued for eleven days while alpha-iodin was given. During this time the pulse averaged 44, with 32 and 60 as extremes. At this point, in spite of improvement, subjective and objective, the patient was obliged to leave the Clinic. A month later his brother, a physician, wrote that he had had no further dizzy spells, but it had been necessary to reduce the dose of alpha-iodin on account of nervous symptoms.

CASE 4 (163,350).—A married woman, aged twenty-five years. No venereal history. Wassermann not taken. She had had repeated attacks of tonsillitis. Three years previously she fell and struck her lower back. The pain was very severe for a week and was then relieved by the discharge of a large quantity of pus through the rectum. A week later she had an attack of tonsillitis, and after a week of illness she began vomiting repeatedly and had repeated fainting spells. A physician was called, who found her pulse 28. There was a fair recovery from symptoms, and the patient was in fair health except for dyspnea for a year. One morning she suddenly fell over and remained unconscious for nearly an hour. During this time she was said to have been very blue and to have had a very slow pulse. Since then, two years before coming to the Clinic, she had had repeated sinking spells with slow pulse, usually brought on by exertion.

Physical Examination.—The heart was 4½ inches to the left and the pulse 42. Blood-pressure, 158–78. The beats were irregular, and there was a faint systolic murmur at the apex, with only slight transmission toward the axilla. The tonsils were moderately enlarged, with marked evidences of chronic tonsillitis. An electrocardiogram on the first day showed a ventricular rate of 60, due to repeated ventricular extrasystoles, with auricles 92.

Treatment.—One-half mgm. alpha-iodin was administered daily. The auricular rate rose within five days to 120 and within nine days to 180.

The ventricular rate averaged 45 to 48. The patient then left the Clinic. Eight months after the beginning of the treatment she wrote: "My health is fine and I am gaining every day. I can do as much work as the average woman and not be very tired either."

In this case there was complete cessation of the Stokes-Adams syndrome for eight months after two years' duration, during which time it had occurred often. Circumstances prevented a closer study of the ventricular rate, but the result seems fairly conclusive when studied with other cases.

In addition to these four cases there have been five other patients observed, but not treated since November 1, 1914. The total number of cases, 3 women and 6 men, may be summarized as follows: One patient was twenty-five, two were in the forties, one in the fifties, and five in the sixties. One gave a history of gonorrhea, none gave histories of syphilis. Six showed negative Wassermanns. Only one patient gave a history of rheumatic fever; 2 others admitted vague rheumatic pains. In 2 instances the trouble seems to have followed diphtheria, and "grip" may have been the etiologic factor in 4. Seven of the 9 patients gave a history of the Stokes-Adams syndrome, and all but one had cardiac murmurs. Three of these showed clinical predominance of an aortic lesion, and 5 predominance of a mitral lesion. Of the 7 patients concerning whom word has been received recently, 3 are dead, all dying in typical Stokes-Adams attacks.

SUMMARY

1. Alpha-iodin quickens the idioventricular rate in complete heart block. This is followed by marked subjective relief to the patient. The drug must be pushed to the tolerance of the patient, and the dose then reduced to the highest dose that can be taken without discomfort. The auricular rate increases much earlier and to a much higher figure proportionately than the ventricular rate.

2. In 9 cases of complete heart block 8 patients gave evidence of definite valvular disease, mitral disease predominating. The ninth patient had advanced nephritis.

3. In none of these 9 cases was there a probable venereal etiology.

4. Six of the patients gave a history of probable etiologic infections with the streptococcic group, i. e., chronic arthritis (1 case), "grip," and tonsillitis (5 cases). Diphtheria seems to have been responsible in two instances. The ninth patient did not give a history of previous infection on careful inquiry, but at autopsy a large, mulberry, calcified nodule was

found involving the bundle and one cusp of the aortic valve. No other pathology was evident.

5. Digitalis should be used in all cases of chronic heart block in which there is evidence of myocardial insufficiency.

6. We do not know the effects of long-continued administration of large doses of alpha-iodin in patients not suffering from thyroid insufficiency; therefore we believe that for the present this medication should be used only to relieve the Stokes-Adams syndrome in chronic heart block.

ISO-AGGLUTINATION GROUPS: DIAGRAM
SHOWING THEIR INTERRELATION *

ARTHUR H. SANFORD

Recently Brem[1] has published a very comprehensive review of his results with his own practical application of Moss'[2] principles. It would seem futile to try to add any information to that presented. Our own experience with Brem's microscopic method has proved its worth conclusively as a time-saving procedure in determining the suitability of donors for transfusion. However, in explaining the Moss agglutination groups to clinicians, we have found that some confusion arises regarding the relation of the four groups unless a careful study has been made of Moss' tables, but that the principles are readily grasped by referring to the accompanying diagram. (See Fig. 293.)

The diagram explains itself. Landsteiner's[3] idea regarding the number of agglutinins is all that is necessary to explain the reaction, if we consider that the serum of Group II contains Agglutinin A, and that of Group III contains Agglutinin B, while Group IV contains both Agglutinin A and Agglutinin B. Group IV then agglutinates the corpuscles of Group II by virtue of its Agglutinin B, and its Agglutinin A acts on the corpuscles of Group III.

Ottenberg's[4] well-known grouping can be applied to the same diagram by merely exchanging the numerals I and IV, as his Group I agglutinates all corpuscles, and there is no agglutinin in his Group IV.

It is preferable, but not always necessary, in transfusion that donor and recipient belong to the same group. The essential for safety is that the serum of the recipient should not agglutinate the corpuscles of the donor. The diagram tells at a glance to what group a person must belong in order to be a suitable donor for an individual of another group. If the arrow points toward the patient's group, and away from the group of the donor, the transfusion may be done without what Brem has called

"anaphylactoid" reaction. It must always be remembered that on the diagonal connecting Groups II and III the arrows point in both directions, and that blood in these reciprocal groups should never be interchanged. It is evident, then, that 100 per cent. of persons can be used as donors for patients of Group I, 83 per cent. for those of Group II,

I (No agglutinin)
(10 per cent. of all persons)

III (1 agglutinin) "B"
(7 per cent. of all persons)

II (1 agglutinin) "A"
(40 per cent. of all persons)

IV (both agglutinins) "A" + "B"
(43 per cent. of all persons)
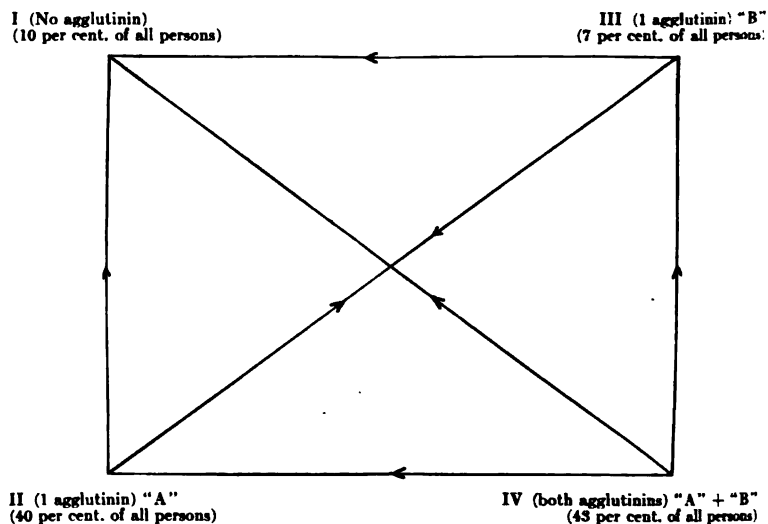
Fig. 293.—Moss agglutination groups: The corpuscles of the various groups are agglutinated by the serums of the groups from which the arrows lead.

and 50 per cent. for those of Group III. For those of Group IV, only 43 per cent. are available as donors, as a patient of this group must have a donor of the same group.

REFERENCES

1. Brem, W. V.: "Blood Transfusion, with Special Reference to Group Tests," Jour. Amer. Med. Assoc., 1916, lxvii, 190–193.
2. Moss, W. L.: "Studies on Iso-agglutinins and Isohemolysins," Bull. Johns Hopkins Hosp., 1910, xxi, 63–70.
3. Landsteiner, K.: "Ueber Agglutinationserscheinungen normalen menschlichen Blutes," Wien. klin. Wchnschr., 1901, xiv, 1132–1134.
4. Ottenberg, R.: "Studies in Iso-agglutination," Jour. Exper. Med., 1911, xiii, 425–438.

THE CYTOLOGY OF NORMAL GOATS' BLOOD *

GEORGINE LUDEN

These observations on the cytology of normal goats' blood are intended as an introduction to studies on the pathologic changes occurring in the blood of goats under certain experimental conditions. I report them herewith that they may furnish data for other workers in this field of research.

The blood of goats does not appear to be a popular subject with hematologists. In literature dealing with the cytology of the blood of animals less than a dozen publications will be found containing data on the blood of goats. In every instance the total number of red corpuscles and white cells alone seems to have been considered worth recording. Differential counts for the blood of normal goats do not seem to have been made, although the pathologic changes following splenectomy have been reported by Warthin.[1]

TOTAL ERYTHROCYTE AND LEUKOCYTE COUNTS

A detailed summary of the total number of erythrocytes and leukocytes found by Malassez,[2] Hayem,[3] Storch,[4] Mohler and Washburn,[5] Wells and Sutton,[6] Warthin[1] and Mann[7] is given in Table 1.

In comparing the figures in this table it should be remembered that the number of the red cells is subject to variations according to the age, the sex, and the breed of the animals used for the counts. Malassez (total, 19,000,000) and Hayem (18,000,000) do not mention these three factors in their report; Storch (kids, 10,000,000; males, 15,000,000; females, 13,000,000) has considered them very carefully, but his data refer to native Swiss goats (the smooth-haired type) and the influence of climate and altitude may have to be taken into account in contrasting them with Mann's observations (males, 16,000,000; females, 17,000,000) made on animals of a similar type (*Capra hircus*).

The average of 9,000,000 to 10,000,000 reported by Mohler and Washburn for Angora goats would appear somewhat low compared with an average of 14,000,000 mentioned by Wells and Sutton, and the total of 13,000,000 and 18,000,000 observed by me in two animals (adults; 1 male, 1 female) of the same breed, although it is well known that there is a marked difference, not only in appearance, but in constitutional hardiness between the Angora and *Capra hircus*, or common goat, the Angora being much more sensitive to outward conditions.

Storch's conclusions that the total number of erythrocytes runs higher in males than in females of the same species, and that kids have a lower average than adult animals, do not seem to be corroborated by the findings of Mann and Wells and Sutton. It must be remembered, however, that Storch's observations were made on a variety of *Capra hircus*, whereas Wells and Sutton studied Angoras. Moreover, Mann's counts (Table 2) clearly show that differences of 4,000,000 to 5,000,000 may be found in one and the same animal within a few days. The range in the total number of red corpuscles from 10,000,000 to 25,000,000 in apparently normal goats suggests that experimental observations based on erythrocyte counts may be extremely deceptive, even when the possibility of technical errors (due to smallness of the red cells and the fact that they may be crowded together in the counting chamber even when a dilution of 1 : 200 is used) has been eliminated so far as possible.

The total leukocyte count in goats presents neither the technical difficulties nor the resulting element of error mentioned above, yet the figures in Table 1 show that variations from 6000 to 18,000 in the number of white cells occur within normal limits. Consequently observations on leukocytosis and allied conditions brought about experimentally are apt to result in erroneous conclusions.

DIFFERENTIAL COUNTS

Differential counts on the contrary appear to furnish constant and reliable data.

Our observations on the differential counts in normal goats will be found in Tables 3 to 10 and may be divided into two groups:

Group A: weekly counts of six normal goats over a period of five to seven weeks.

Group B: daily counts of two goats taken during two weeks.

The total number of counts made was 51; in every instance 200 cells were counted, the total number of cells that came under observation

TABLE 1.—ERYTHROCYTES AND LEUKOCYTES IN THE BLOOD OF GOATS
GOATS—(NATIVE SWISS SPECIES)
STORCH, A*

No	SEX	ERYTHROCYTES	LEUKOCYTES	PROPOR-TION	PREG-NANT	ERYTHROCYTES	LEUKO-CYTES	PROPOR-TION
5	M	15,300,000	11,520	1374	..	..	..	..
8	F	13,839,000	12,594	1108	4	14,258,000	11,229	1272
8	K	10,151,000	11,358	827	..	..	..	..

ANGORA GOATS
WELLS, J. J., AND SUTTON, J. E.†

	ERYTHROCYTES	LEUKOCYTES
Suckling kid...............................	11,748,000	6,600
Milch......................................	11,220,000	..
Suckling kid...............................	19,760,000	8,000
Milch......................................	16,970,000	..
Male, 76 days old.........................	19,376,000	12,250
Male, 69 days old.........................	22,344,000	12,500
Average adult.............................	14,974,000	7,300
Average kid...............................	20,864,000	12,525

ANGORAS—NORMAL
MOHLER, J. R., AND WASHBURN, H. J.‡

No.		ERYTHROCYTES	LEUKOCYTES
9	Average...............................	10,000,000	9,200

CAPRA HIRCUS
MANN, F.

	ERYTHROCYTES	LEUKOCYTES
Male, 23 counts, Average...................	16,072,000	13,110
Female, 17 counts, Average.................	17,183,000	14,350

ANGORAS—NORMAL
LUDEN, G.

	ERYTHROCYTES	LEUKOCYTES
Male (Goat 10)............................	13,400,000	8,140
Female (Goat 35)..........................	18,800,000	11,200

CAPRA HIRCUS
WARTHIN, A. S.§

	ERYTHROCYTES	LEUKOCYTES
Average....................................	16,000,000	8,000

* Inaugural Dissertation, Bern, 1901.   † Amer. Jour. Physiol., 1915, xxxix, 31–36.
‡ Bulletin 45, Bureau of Animal Industry, 1903.   § Jour. of Med. Res., 1902, xii, 457.

'16—42

TABLE 2.—ERYTHROCYTES, LEUKOCYTES, AND HEMOGLOBIN IN THE
BLOOD OF NORMAL GOATS (MANN)

GOAT 5—(MALE, CAPRA HIRCUS)

DATE, 1915	ERYTHROCYTES	LEUKOCYTES	HEMOGLOBIN. PER CENT.
7–29	17,125,000	13,000	Not given

GOAT 9—(FEMALE, CAPRA HIRCUS)

DATE, 1915	ERYTHROCYTES	LEUKOCYTES	HEMOGLOBIN. PER CENT.
7–29	16,700,000	9,800	..
8– 3	18,635,000	15,700	..
8–11	19,125,000	15,400	..
8–18	18,862,000	15,400	..
8–26	19,337,000	14,900	99
9– 1	19,275,000	13,800	97
9– 7	18,760,000	13,500	..
9–16	19,500,000	14,750	95
9–24	17,285,000	12,000	90
9–29	21,735,000	14,850	90
9–30	19,300,000	14,475	78
10– 1	20,475,000	14,000	80
10–12	16,550,000	14,300	70
10–20	16,850,000	13,000	..
10–27	18,350,000	18,450	..
11– 3	18,700,000	15,750	..
11– 8	20,800,000	12,000	.

GOAT 6—(MALE, CAPRA HIRCUS)

DATE, 1915–16	ERYTHROCYTES	LEUKOCYTES	HEMOGLOBIN. PER CENT.
7–29	20,000,000	13,100	..
7–30	....	......	..
8– 3	18,200,000	14,600	..
8–11	19,012,000	11,500	.
8–19	19,062,000	14,250	..
8–26	19,063,000	15,600	..
9– 5	19,237,000	13,000	98
9– 8	19,250,000	15,200	..
9–22	23,975,000	11,650	85
9–24	19,000,000	16,650	95
9–28	19,700,000	13,300	85
9–30	18,450,000	15,650	82
10– 6	17,800,000	14,000	87
10–14	21,050,000	13,950	90
10–20	17,800,000	12,750	70
11– 3	21,950,000	17,000	..
11–10	19,100,000	17,900	.
11–17	20,500,000	16,300	80
11–23	23,050,000	15,150	..
12– 3	20,200,000	8,100	80
12–10	20,000,000	15,850	75
12–17	19,950,000	18,700	80
12–22	19,950,000	12,000	80
1– 3	24,350,000	11,550	90

TABLE 3.—WEEKLY DIFFERENTIAL COUNTS—GOAT 16 (GROUP A)

Results expressed in per cent.

Sex	Age Months	Breed	Description	Weight Kg	Date of Count 1915	Polymorpho-nuclear Clear Leucocytes	Small Lymphocytes	Large Lymphocytes	Eosinophile Leucocytes	Mast Cells	Transitionals	Myelocytes	Normoblasts	Tork's Irritation Cells	Atypical Lymphocytes	Tumor 1	Tumor 2	Cholesterol
M	5	Common	Coarse white hair mixed with gray	13.4	9/16	56.0	21.0	13.5	0.0	1.5	6.0	2.0	0	0.0	0	0	0	..
					10/18	56.5	36.0	6.0	0.5	0.0	1.0	0.0	0	0.0	0	0	0	0.17
					10/21	53.5	27.0	13.0	1.5	1.5	2.0	1.0	0	0.0	0	0	0	0.194
					10/25	54.5	33.5	5.5	0.5	1.0	1.5	0.5	0	1.0	0	0	0	0.112
					10/28	52.5	37.0	7.0	1.5	1.0	0.0	1.0	0	0.5	0	0	0	0.09
					11/8	54.0	31.0	12.0	0.0	1.0	0.5	0.0	0	0.5	0	0	0	0.112
					Average	54.5	31.3	9.5	0.7	1.0	1.8	0.8	0	0.3	0	0	0	0.103

TABLE 4.—WEEKLY DIFFERENTIAL COUNTS—GOAT 17 (GROUP A)

Results expressed in per cent.

Sex	Age Months	Breed	Description	Weight Kg	Date of Count 1915	Polymorpho-nuclear Clear Leucocytes	Small Lymphocytes	Large Lymphocytes	Eosinophile Leucocytes	Mast Cells	Transitionals	Myelocytes	Normoblasts	Tork's Irritation Cells	Atypical Lymphocytes	Tumor 1	Tumor 2	Cholesterol
F	4	Common	Coarse white and cream. Maltese type	14.5	9/16	48.5	34.5	14.0	0.5	1.0	0.5	6.0	0.0	0.0	0	0	0	..
					10/13	24.5	61.0	22.0	1.5	1.0	1.0	0.0	0.0	0.0	0	0	0	0.119
					10/18	42.0	51.5	4.5	0.0	0.5	1.5	0.0	0.0	0.0	0	0	0	0.112
					10/21	42.5	50.5	2.0	3.5	0.5	0.0	0.5	0.0	0.5	0	0	0	0.07
					10/25	48.5	44.0	6.0	2.5	0.5	0.0	3.5	0.0	0.0	0	0	0	0.13
					10/28	33.5	40.5	9.5*	11.0	2.0	2.0	0.5	0.0	1.0	0	0	0	0.13
					11/8	35.0	41.0	15.5	2.0	1.0	2.5	2.5	0.5	1.0	0	0	0	
					Average	37.8	46.1	10.5	3.3	0.9	1.1	1.9	0.07	0.4	0	0	0	0.801

* Two mitoses.

TABLE 5.—WEEKLY DIFFERENTIAL COUNTS—GOAT 19 (GROUP A)

Results expressed in per cent.

Sex	Age, Months	Breed	Description	Weight, Kg.	Date of Count, 1915	Polymorpho-nuclear Leucocytes	Small Lymphocytes	Large Lymphocytes	Eosinophile Leucocytes	Mast Cells	Transitionals	Myelocytes	Normoblasts	Türk's Irritation Cells	Atypical Lymphocytes	Tumor 1	Tumor 2	Cholesterol
M	5	Common	Coarse yellowish hair	12.7	10/13	18.0	42.0	39.0	1.5	0.0	2.5	1.0	0	0	0	0	0	0.17
					10/18	36.5	40.5	18.0	1.5	1.5	2.0	0.0	0	0	0	0	0	0.10
					10/21	33.5	49.0	17.0	0.0	0.0	0.0	0.5	0	0	0	0	0	0.094
					10/25	51.0	39.0	17.5	0.0	0.5	2.0	0.0	0	0	0	0	0	0.112
					10/28	38.5	47.5	12.0	0.5	1.0	0.5	0.0	0	0	0	0	0	0.168
					Average	35.5	41.6	20.7	0.7	0.6	1.4	0.3	0	0	0	0	0	0.129

TABLE 6.—WEEKLY DIFFERENTIAL COUNTS—GOAT 20 (GROUP A)

Results expressed in per cent.

Sex	Age, Months	Breed	Description	Weight, Kg.	Date of Count, 1915	Polymorpho-nuclear Leucocytes	Small Lymphocytes	Large Lymphocytes	Eosinophile Leucocytes	Mast Cells	Transitionals	Myelocytes	Normoblasts	Türk's Irritation Cells	Atypical Lymphocytes	Tumor 1	Tumor 2	Cholesterol
M	4	Common	Silky white hair	12.4	9/16	41.0	45.0	12.0	0.5	0.5	1.0	1.0	0	0.0	0.0	0	0	....
					10/13	38.0	30.5	23.0	1.5	0.0	1.0	0.5	0	0.0	0.0	0	0	0.114
					10/18	27.5	56.0	14.5	0.0	0.5	1.0	0.0	0	1.0	1.0	0	0	0.090
					10/21	48.5	32.5	8.5	1.5	2.5	1.0	5.5	0	0.0	1.0	0	0	0.084
					10/25	46.5	35.5	17.0	1.5	0.0	0.5	0.0	0	0.0	0.0	0	0	0.112
					10/28	42.0	40.0	15.0	1.0	1.0	3.5	0.0	0	0.5	0.0	0	0	0.134
					11/8	51.0	28.5	5.0	11.0	0.5	1.0	0.0	0	0.5	0.0	0	0	
					Average	42.1	38.3	13.3	2.6	0.7	1.2	0.0	0	0.2	0.3	0	0	0.031

TABLE 7. WEEKLY DIFFERENTIAL COUNTS GOAT 21 (GROUP A)

Results expressed in per cent.

Sex	Age, Months	Breed	Description	Weight, Kg.	Date of Count, 1915	Polymorpho-nuclear Leucocytes	Small Lymphocytes	Large Lymphocytes	Eosinophile Leucocytes	Mast Cells	Transitionals	Myelocytes	Normoblasts	Türk's Irritation Cells	Atypical Lymphocytes	Tumor 1	Tumor 2	Cholesterol
M	5	Common	Coarse white hair	13.1	9/16	24.0	70.5	1.5	0.0	1.5	0.0	2.0	0	0	0	0	0	·:··
					10/4	28.0	50.0	7.5	0.0	1.0	2.0	1.5	0	0	0	0	0	0.124
					10/18	30.0	60.5	7.5	1.0	1.0	0.0	0.0	0	0	0	0	0	0.084
					10/21	31.0	58.5	9.5	0.0	0.0	0.0	1.0	0	0	0	0	0	0.078
					10/25	38.0	58.5	5.5	0.0	1.0	1.0	1.0	0	0	0	0	0	0.07
					10/28	54.5	30.5	5.5	2.0	5.0	3.0	0.0	0	0	0	0	0	0.072
					Average	35.9	58.9	6.2	0.5	1.6	1.0	0.9	0	0	0	0	0	0.071

TABLE 8.—WEEKLY DIFFERENTIAL COUNTS—GOAT 26 (GROUP A)

Results expressed in per cent.

Sex	Age, Months	Breed	Description	Weight, Kg.	Date of Count, 1915	Polymorpho-nuclear Leucocytes	Small Lymphocytes	Large Lymphocytes	Eosinophile Leucocytes	Mast Cells	Transitionals	Myelocytes	Normoblasts	Türk's Irritation Cells	Atypical Lymphocytes	Tumor 1	Tumor 2	Cholesterol
M	4	Common	Coarse white and black hair	10.6	10/13	36.0	31.0	20.5	5.0	0.5	1.5	5.5	0.0	0	0	0	0	0.146
					10/18	37.5	38.5	17.5	2.0	3.0	1.5	0.0	0.0	0	0	0	0	0.09
					10/21	34.5	47.5	7.5	5.5	0.5	2.0	2.5	0.0	0	0	0	0	0.09
					10/25	41.0	42.0	9.5	2.0	5.5	0.0	0.0	0.0	0	0	0	0	0.10
					10/28	46.0	40.0	7.5	2.0	2.0	2.0	0.0	0.0	0	0	0	0	0.10
					11/8	40.5	23.0	20.5	4.0	3.0	8.0	0.5	0.5	0	0	0	0	0.13
					Average	39.3	37.0	13.8	3.4	2.4	2.5	1.4	0.08	0	0	0	0	0.109

TABLE 9.—DAILY DIFFERENTIAL COUNTS—GOAT 10 (GROUP B)
Results expressed in per cent.

Sex	Age, Months	Breed	Description	Date of Count, 1915	Polymorpho-nuclear Leucocytes	Small Lymphocytes	Large Lymphocytes	Eosinophile Leucocytes	Mast Cells	Transitionals	Myelocytes	Normoblasts	Irritation Cells Török's*	Atypical Lymphocytes	Tumor I	Tumor 2	Megaloblasts	Large Mononuc- lears Clears
M	12	Angora	Black and white	3/3	35.0	35.5	15.0	4.0	4.0	7.0	1.5	0.0	1.0	0.0	0	0	0.0	0.0
				3/4	33.0	25.5	8.0	12.5	3.0	6.5	0.0	0.0	1.5	10.0	0	0	0.0	0.0
				3/6	32.0	22.5	7.0	8.5	1.0	7.5	0.0	0.0	2.5	19.5	0	0	0.0	0.0
				3/7	35.0	33.0	14.5	8.5	4.0	2.5	1.5	1.0	0.0	1.5	0	0	0.0	0.0
				3/8	27.5	33.5	13.5	14.5	2.0	1.5	0.0	1.0	1.0	5.5	0	0	0.0	0.0
				3/9	26.0	30.0	12.0	11.0	2.5	6.0	0.5	0.0	2.5	9.0	0	0	0.5	0.5
				3/10	33.5	31.0	14.5	6.0	1.0	1.5	1.0	0.0	0.0	10.0	0	0	0.0	0.0
				3/13	56.0	28.5	5.0	2.0	2.0	3.5	0.0	0.0	0.5	2.5	0	0	0.0	0.0
				3/14	45.0	33.0	12.0	10.0	1.0	2.5	0.0	0.0	0.0	2.5	0	0	0.0	0.0
				3/15	35.0	40.5	12.0	4.0	3.0	1.0	0.0	0.0	1.0	3.5	0	0	0.0	0.0
				3/16	35.0	23.5	15.5	9.5	2.5	1.0	0.0	2.5	0.0	10.5	0	0	0.0	0.0
				3/17	36.5	13.5	15.0	6.0	2.0	3.0	1.0	0.0	1.0	22.5	0	0	0.0	0.0
				3/18	35.5	32.0	17.5	6.5	2.0	2.5	0.5	0.5	0.0	2.5	0	0	0.0	0.0
				3/20	34.0	21.0	18.0	3.5	1.0	4.5		0.5	0.5	16.0	0	0	0.0	0.0
				Average	35.6	28.1	12.8	7.6	2.2	3.6	0.4	0.4	0.8	8.3	0	0	0.07	0.04

* February 28: Hemoglobin, 55 per cent.; erythrocytes, 13,400,000; leukocytes, 8,140.

TABLE 10.—DAILY DIFFERENTIAL COUNTS—GOAT 35 (GROUP B)

Results expressed in per cent.

Sex	Age, Months	Breed	Description	Date of Count, 1915*	Polymorpho-nuclear Leucocytes	Small Lymphocytes	Large Lymphocytes	Eosinophile Leucocytes	Mast Cells	Transitionals	Myelocytes	Normoblasts	Türk's Irritation Cells	Atypical Lymphocytes	Tumor 1	Tumor 2	Megaloblasts	Large Mononu-clears
F	12	Angora	White	3/ 3	36.5	29.0	9.5	6.0	7.5	4.5	4.0	2.0	0.0	1.0	0	0	0.0	0.0
				3/ 4	41.0	24.5	14.0	7.5	6.0	3.0	4.0	0.0	0.0	0.0	0	0	0.0	0.0
				3/ 6	22.0	37.5	17.5	7.5	5.0	6.0	4.0	0.0	0.0	0.5	0	0	0.0	0.0
				3/ 7	28.0	25.5	17.0	9.0	6.0	2.0	4.0	1.5	0.0	2.5	0	0	4.0	0.0
				3/ 8	33.0	30.0	13.0	5.5	3.0	3.5	1.0	0.0	0.0	6.0	0	0	0.0	0.0
				3/ 9	38.0	26.0	11.5	5.5	1.5	3.5	0.0	0.0	0.5	18.5	0	0	0.5	0.0
				3/10	37.0	27.0	15.0	4.5	2.5	4.0	2.5	1.0	1.0	0.0	0	0	0.0	0.0
				3/13	37.5	33.0	13.0	7.0	2.0	6.0	2.0	0.0	0.0	0.0	0	0	0.0	0.0
				3/14	48.0	28.0	10.0	2.0	3.0	7.5	0.0	2.0	1.5	0.0	0	0	0.0	0.0
				3/15	40.5	25.0	17.5	3.0	4.0	2.5	0.0	0.0	0.0	0.5	0	0	0.0	0.0
				3/16	40.5	33.0	13.0	2.5	3.5	2.5	0.5	2.5	0.5	4.0	0	0	0.0	0.0
				3/17	35.5	45.0	14.0	6.0	2.5	2.5	0.0	2.0	0.0	1.0	0	0	0.0	0.0
				3/18	36.0	31.0	16.0	8.0	3.0	5.5	2.5	0.0	0.0	1.5	0	0	0.0	0.0
				3/20	35.0	23.0	7.5	1.5	4.0				1.5	17.5	0	0	0.0	2.0
				Average	36.3	29.1	13.5	5.4	3.8	4.0	1.8	0.8	0.4	3.4	0	0	0.3	0.1

* February 28: Hemoglobin, 70 per cent.; erythrocytes, 18,800,000; leukocytes, 11,200.

being 10,200. In addition, differential counts were made for a number of animals not belonging to our series. These, however, have not been recorded in the tables, either because the animal had been used for some experiment, and for that reason its blood could no longer be safely considered "normal," or because it died or was sacrificed after only a few counts had been made. In either case the data obtained were too meager to be considered conclusive, though it should be stated that the differential counts of these animals were not found to differ materially from those recorded in our tables.

TECHNIC

Three blood-smears were used for each count. The smears were made on slides in preference to cover-slips for several reasons: (1) It was found advisable to write the number of the animal and the date of counting on each slide to prevent confusion while staining and for future reference; (2) the "slide method" obviates the use of Canada balsam, which cannot be dispensed with if cover-slips are used and which has a tendency to destroy the color of anilin dyes; and (3) owing to the war, cover-slips could not be procured in sufficient numbers.

The blood-smears were stained by the Jenner, the Harlow-Hayhurst, and the Pappenheim methods, additional slides being stained at intervals with the Leishman stain for the sake of comparison. As has been stated, a differential count of 200 cells was made uniformly, the result being expressed in per cent. to permit of an easy comparison with the current clinical data on blood counts. Special attention was given to the fact that the smaller types of cells (small lymphocytes, normoblasts) showed a tendency to congregate at one end of the slide (presumably because of their specific gravity), whereas greater numbers of the larger types were generally found at the opposite end. In order to minimize this factor of error as much as possible several areas were counted on each slide, the total count of 200 cells being made from three slides each time.

TERMINOLOGY

Ehrlich's terminology has been used in all our counts, but the various types of leukocytes have been recorded in sequence of their relative numeric frequency. Although this classification cannot be considered correct from a hematologic point of view, it is generally found in clinical reports and has been adopted to facilitate the comparison between our data and clinical observations. For the same reason the term "poly-

morphonuclear" has been retained in preference to the term "ampho-
phile" used by Kanthack, Bunting, and Warthin for animal counts.
According to Brinkerhoff and Tyzzer,[8] the amphophile leukocyte in rab-
bits "is the equivalent of the neutrophile leukocyte of human blood";
in normal goats' blood it is indistinguishable from the human polymor-
phonuclears when stained with azur dyes. The exact staining reaction
of the granules found in the polymorphonuclears of the goat will be
determined later, for though these granules take a bluish tint in the
Jenner and the Harlow-Hayhurst stain similar to that found in the
human cell under similar conditions (a purplish-brown tone being seen
in slides stained according to the Pappenheim or the Leishman method
for both species), the color reaction may not be truly "neutrophile" in
character. Until the nature of the granules has been definitely estab-
lished (the investigation had to be postponed on account of the scarcity
of histologic dyes), it seems permissible to employ the term "polymor-
phonuclears," since it is often used in clinical literature for this type of
cell and would therefore make a comparison more convenient between
the changes observed in goats' blood under experimental conditions and
in human blood under certain conditions of disease.*

The words "transitionals" and "atypical lymphocytes" in our termi-
nology require a few words of explanation. "Transitional" has been
used deliberately in preference to "large mononuclear," as the cells of
this type found in normal goats' blood invariably belonged to that sub-
division of the mononuclears called "transitionals" by Ehrlich, Gra-
witz,[9] Karl Schleip,[10] Leishman, Meyer and Rieder,[11] and others: That
is to say, the cells in question all answered the following description:[12]
"These cells resemble in a general way the preceding (large mononu-
clears), but are differentiated from them by a large indentation of the
nucleus, which frequently gives it the form of a wallet, by a somewhat
greater affinity of the nucleus to nuclear dyes, and by the presence of a
number of neutrophile granulations in the protoplasm." The typical
mononuclears "with a large, oval, usually eccentrically situated and
feebly staining nucleus, and a relatively large amount of protoplasm"[12]

* Since sending this communication to print the following statement has been received
from Professor Hal Downey, Minneapolis, whom the writer had consulted upon this point:
    "It seems to me that you will be quite safe in calling the polymorphonuclear leuko-
cytes 'neutrophiles.' They certainly show the specific reaction with triacid, although their
poor staining in Wright's stain (Romanowsky mixture) shows that they are not chemically
identical with the granules of the human polymorphonuclears. However, they are suffi-
ciently close to them to be included in the same classification. I see only one type of those
cells in the goats' blood. Eosinophiles and mast-cells seem to be about the same as those
of human blood."

began to appear only at a later period, together with other pathologic changes which will be discussed in another article, and it was therefore considered advisable to reserve the term "mononuclear" for these cells in particular.* The term "atypical lymphocytes" is merely descriptive. The cells referred to are slightly larger than red corpuscles, do not show any trace of protoplasm, and possess a strong affinity for all nuclear dyes. The entire mass of the cell appears to be composed of coarser and finer basophilic granules—occasionally a few granules take a slightly reddish tinge. Considering this total absence of protoplasm, they do not seem to belong to the so-called "small neutrophile *pseudo*-lymphocytes" described by Ehrlich and Lazarus,[12] as these authors state that the latter possess "a small amount of protoplasm studded with neutrophile granulations" and that "the small amount of protoplasm, and the small size of the cell itself, prevent confusion with small myelocytes." The distinctly granular character of the entire cell-body and the fact that stages of transition between these cells and the small lymphocytes could be repeatedly observed make it seem probable that they are the "bare" nuclei of small lymphocytes, which, according to Downey, have been "stripped of their protoplasm by some unknown cause"; their granular appearance and affinity for basic dyes "being accounted for as due to pyknotic changes occurring in the nuclei themselves."† These atypical lymphocytes were not found in the counts of the six normal goats (Group A), but increased in numbers as the blood-picture began to show pathologic changes. It will be noted, however, that these cells do occur in Group B (Angora goats). As the blood-smears of these counts were made after a spell of intensely cold weather, and also as chemical changes (*i. e.*, a slight increase of the cholesterol value) were observed in the blood of our animals during this period, it is possible that some slight disturbance of metabolism due to the cold may have been responsible for the appearance of the abnormal cells in an otherwise normal blood-picture. All the goats appeared to be in perfect health at the time.

MORPHOLOGY

There is little to be said about the general morphology of blood-cells in normal goats. It is well known that the red corpuscles are much

---

* The descent and ultimate fate of transitionals and mononuclears will not be taken into account in this paper, as it is intended for experimental purposes only and does not aspire to dealing with hematology as a science, especially since, according to Grawitz, "no two hematologists so far have been found to agree on the question."

† Personal communication.
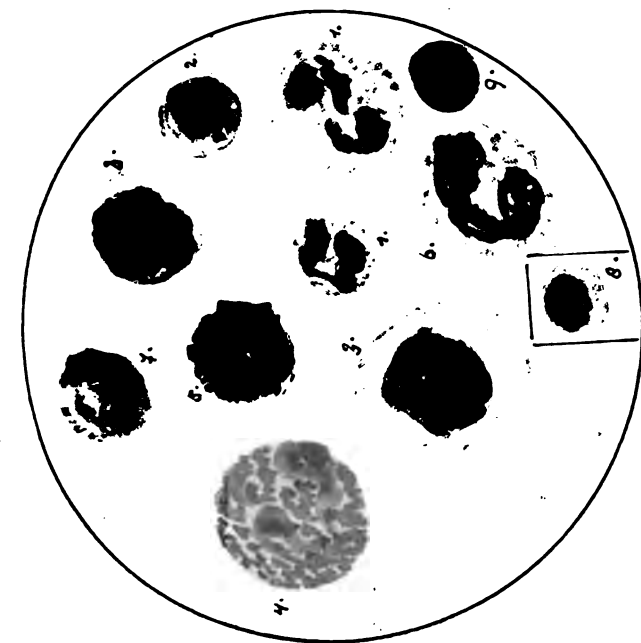
Fig. 294

Normal Human Blood..........$\left\{ \begin{array}{l} \textit{Pappenheim stain} \\ \textit{Zeiss camera lucida} \end{array} \right\}$..........Normal Goats' Blood

Fig. 295

1. Polymorphonuclear leukocyte.
2. Small lymphocyte.
3. Large lymphocyte.

4. Eosinophile leukocyte.
5. Mast cell.
6. Transitional.
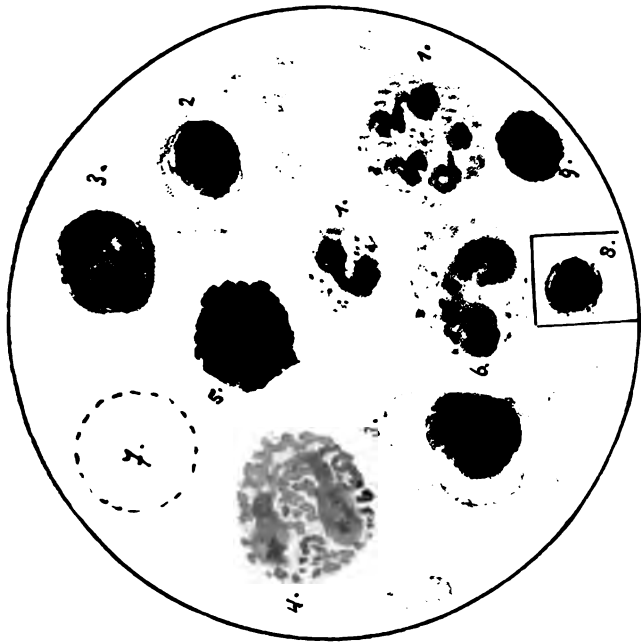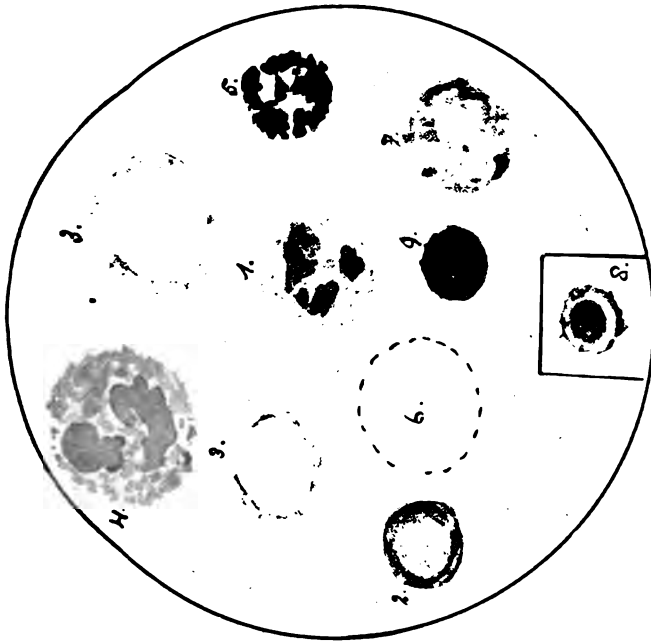
7. Neutrophile myelocyte.
8. Normoblast.
9. Atypical lymphocyte.

Fig. 296

Fig. 297

Normal Human Blood .... { *Harlow-Hayhurst stain* } .... Normal Goats' Blood.
                                       { *Zeiss camera lucida* × 700 }

1. Polymorphonuclear leukocyte.   4. Eosinophile leukocyte.   7. Neutrophile myelocyte.
2. Small lymphocyte.   5. Mast cell.   8. Normoblast.
3. Large lymphocyte.   6. Transitional.*   9. Atypical lymphocyte.

* The blank circle here indicates that no cell of corresponding type was found in eight slides of this blood examination.

smaller than those found in man, the average size given by Ellenberger[13] being 4.1 μ. (Human type, average size, 7 μ.) Poikilocytosis and aniso-cytosis are often observed in apparently normal animals, but to a certain extent may be due to the inevitable crowding together of the corpuscles. The only cell differing materially from the corresponding cell-types seen in human blood is the normoblast. Its characteristics are those of a basophilic nucleated corpuscle. With the Pappenheim stain it assumes a tint of intense dark blue comparable to the "Prussian blue" in water-color. The edge of the cell stains somewhat lighter and has the appear-ance of being slightly curled up. Occasionally there are found on this edge a few tiny granules which are gold-brown in color and appear to be a part of the cell. The shape of the normoblast is usually round, but oval forms also may be found.

The leukocytes, as has already been stated with reference to the poly-morphonuclears, are indistinguishable both in morphology and staining reaction from their human equivalents with the usual staining methods (Jenner, Giemsa, Pappenheim, Harlow-Hayhurst, or Leishman). As these stains are generally used in clinical hematology, and it seemed desirable to adhere as closely as possible to clinical methods for reasons stated above, my observations on the striking similarity between the white cells in human and in goats' blood refer to these staining methods only, though it is possible that there may be a slight cytologic difference which could be made visible by special methods. However, as the main object of this paper is to furnish data of comparison for those who wish to use goats in experimental work, cytologic details which may be of interest to hematologists, but do not play a prominent part in the clinical valuation of the blood-picture, have not been taken into consideration. The striking similarity between normal leukocytes in man and the leuko-cytes in normal goats' blood is clearly demonstrated by the colored plates (Figs. 294–297).

AVERAGE NUMBERS OF THE VARIOUS TYPES OF CELLS FOUND IN NORMAL GOATS

Whereas a detailed account of the relative frequency with which the various types of cells occur in normal animals may be found in Tables 3 to 10, the average percentage for each individual animal appears to be as follows:

Goat No.	Poly-morphonuclear Leukocytes	Small Lymphocytes	Large Lymphocytes	Eosinophile Leukocytes	Mast Cells	Transitionals	Myelocytes	Normoblasts	Türk's Irritation Cells	Atypical Lymphocytes	Megaloblasts
Weekly Counts:											
16	54.5	31.3	9.5	0.7	1.0	1.8	0.8	0	0.3	0	0
17	37.8	46.1	10.5	3.3	0.9	1.1	1.9	0.07	0.4	0	0
19	35.5	41.6	20.7	0.7	0.6	1.4	0.3	0	0	0	0
20	42.1	38.3	13.6	2.4	0.7	1.2	0.9	0	0.2	0	0
21	35.9	53.9	6.2	0.5	1.6	1.0	0.9	0	0	0	0
26	39.3	37.0	13.8	3.4	2.4	2.5	1.4	0.08	0	0	0
Daily Counts:											
35A	36.3	29.1	13.5	5.4	3.8	4.0	1.8	0.8	0.4	3.4	0.3
X	35.6	28.1	12.8	7.6	2.2	3.6	0.4	0.4	0.8	8.3	0.07
Total average	39.6	38.7	12.6	3.0	1.7	2.1	1.1	0.2	0.3	1.5	0.05

As shown by this summary, the average percentages found in 51 differential counts for normal goats proved to be:

	Average, 51 Counts Per Cent.	High Limit, Per Cent.	Low Limit, Per Cent.
Polymorphonuclear leukocytes	40.3	56.5	35.6
Small lymphocytes	35.6	53.0	28.5
Large lymphocytes	12.7	20.6	6.0
Eosinophile leukocytes	2.8	7.4	0.5
Mast cells	1.6	3.7	0.6
Transitionals	2.0	4.0	0.8
Neutrophile myelocytes	0.9	2.1	0.2
Normoblasts	0.1	0.5	0.0
Türk's irritation cells	0.2	0.9	0.0
Atypical lymphocytes	1.3	8.0	0.0

CONDITIONS UNDER WHICH OBSERVATIONS WERE MADE

The goats used for these differential counts may be considered very fair representatives of the average laboratory animal. They were purchased in Texas, where they had been on free range. The six animals used for the weekly counts had lived under laboratory conditions for two weeks when our counts were started. As neither the change of climate and food nor the lack of liberty and exercise appears to have influenced the blood-picture to any considerable extent, the goats may be called "normal" as far as this term can be applied to any animal living in captivity, however favorable the conditions. For the weekly counts the common type of goat (*Capra hircus*) was used; of these animals, one was a female, the others males. For the daily counts I used two typical

Angora goats, one male and one female, that had lived under laboratory conditions for seven months. The ages of our animals could not be determined with absolute accuracy, but are estimated at five months for the six common goats and approximately twelve months for the two Angoras, so that whereas the former must still be considered kids, the latter may be called young adult animals.

During the third week of counting five of the six common goats developed slight symptoms of mange. The disease remained confined to small areas on the nose and ears, and cleared up in about two weeks on the application of a mixture of sulphur and vaselin. No changes were found in the blood-picture during this period of extraneous parasitic infection, a fact recalling Washburn's statement that even intestinal parasites do not seem to alter the cytology of goats' blood, since various types of parasites are often found at necropsy in apparently normal animals. It will be remembered that in a number of cases the human blood-picture has also remained unchanged, although symptomatic evidence had corroborated the diagnosis of intestinal parasites.

The data furnished by my observations may be briefly summarized as follows:

1. Differential counts show that the blood-picture in normal goats is subject to only slight variations.

2. The blood-picture in kids or young adults* does not seem to be materially influenced by either the breed or the sex of the animal.

3. Extraneous parasitic infection (mange) does not change the blood-picture in any way, and various types of intestinal parasites do not appear to alter it to any considerable extent since at necropsy intestinal parasites are found in the greater number of apparently normal goats.

4. The stability of the blood-picture seems to warrant the conclusion that goats are particularly well fitted for cytologic observations and that changes in the differential count caused by experimental conditions can hardly be considered accidental.

5. The similarity in both morphology and staining reaction between the leukocytes in the blood of man and in the blood of normal goats would seem to make it permissible to compare the changes occurring in the human blood-pictures in disease and the pathologic changes observed in the blood of goats under experimental conditions.

* Old goats will be made a subject of future study.

REFERENCES

1. Warthin, A. S.: "The Changes Produced in the Hemolymph Glands of the Sheep and Goat by Splenectomy, Hemolytic Poisons, and Hemorrhage," Jour. Med. Research. 1902, vii, 435–463.

2. Malassez, L. C.: Compt. rend. Acad. d. sc., 1872. Quoted by Storch, *loc. cit.*

3. Hayem, G.: Du sang et de ses altérations anatomiques, Paris, Masson, 1889. Quoted by Storch, *loc. cit.*

4. Storch, A.: Untersuchungen über den Blutkörperchengehalt des Blutes der landwirtschaftlichen Haussäugethiere, Karlsruhe, Machlot, 1901.

5. Mohler, J. R., and Washburn, H. J.: Takosis, a Contagious Disease of Goats, U. S. Bur. Animal Indus., Washington, 1903, Bull. No. 45.

6. Wells, J. J., and Sutton, J. E.: "Blood Counts in the Frog, the Turtle and Twelve Different Species of Mammals," Amer. Jour. Physiol., 1915, xxxix, 31–36.

7. Mann, F. C.: Unpublished data.

8. Brinckerhoff, W. R., and Tyzzer, E. E.: "On the Leukocytes of the Circulating Blood of the Rabbit," Jour. Med. Research, 1902, vii, 173–189.

9. Grawitz, E.: Klinische Pathologie des Blutes, Leipzig, Thieme, 1911, p. 214.

10. Schleip, K.: Atlas der Blutkrankheiten nebst einer Technik der Blutuntersuchungen, Berlin, Urban, 1907, p. 30.

11. Meyer, E., and Rieder, H.: Atlas der klinischen Mikroskopie des Blutes, Leipzig, Vogel, 1907, pp. 21, 31, 33.

12. Ehrlich, P., and Lazarus, A.: "Anemia. Histology of the Blood, Normal and Pathologic," Nothnagel's Encyclopædia of Practical Medicine, Phila., Saunders, 1905, pp. 65, 66, 70.

13. Ellenberger, W., and Baum, H.: Handbuch der vergleichenden Anatomie der Hausthiere, Berlin, Hirschwald, 1900, vol. 2.

OBSERVATIONS ON THE CHANGES IN THE CHOLESTEROL CONTENT OF THE BLOOD OF GOATS, FOLLOWING CHOLESTEROL FEEDING ALONE, ROENTGEN TREATMENT ALONE, AND CHOLESTEROL FEEDING COMBINED WITH ROENTGEN TREATMENT AND SUBSEQUENT CASTRATION *

GEORGINE LUDEN

— — -

The importance of cholesterol metabolism has been established by the work of Weltmann,[1] Bacmeister and Havers,[2] Aschoff,[3] McNee,[4] Wacker,[5] Sternberg,[6] Rothschild,[7] and others; that its study is becoming a subject of general interest may be seen from the number of observations that have been made within the last two years.

While the main object of the earlier work done on cholesterol was the experimental reproduction of the arteriosclerotic lesions (Stuckey,[8] Wesselkin,[9] Chatalow,[10] Anitschkow,[11] and lately McMeans[12]), this work proved incidentally that a great number of organs are affected by a disturbance of the cholesterol balance. Subsequent investigations have shown that the organs principally concerned with the regulation of the cholesterol metabolism are the adrenals, the liver, the genital glands, and the intestines (Rothschild,[7] Weltmann and Biach,[13] Anitschkow and Chatalow,[14] Albrecht and Weltmann,[15] Stewart,[16] Hueck,[17] Gardner and Lander,[18] Sternberg,[6] Löwenthal,[19] McMeans,[12] McNee[4]). That cholesterol is also stored in the body fat has been demonstrated by Rothschild[20] and Wacker.[5] It has further been shown that the cholesterol content of the blood is changed by physiologic as well as by pathologic conditions; that pregnancy and lactation, diseases of the liver, and malignant growths increase cholesterol value, but that the influence of bacterial infection depends on the acute or chronic character of the

process; Weltmann[1] found that in tuberculosis, for instance, the cholesterol content of the blood was lowered as the disease progressed.

The effect of cholesterol on cell proliferation has been made a subject of recent investigations: Robertson and Burnett[21] reported that a growth of transplanted carcinoma in white rats (Flexner-Jobling type) was accelerated by the intravenous injections of cholesterol emulsion; Browder[22] states that the rate of cell division of paramecia is markedly increased by the addition of small amounts of cholesterol to the culture-medium; McMeans[12] observed that proliferation of the arterioles of the lungs and the kidneys occurred in cholesterol-fed rabbits. The bearing of these experiments on the problem of malignant growth is obvious.

The foregoing brief review shows that a great number of factors influence cholesterol metabolism; viz., the relative adequacy of some four or five organs taking part in the regulation of the metabolic balance and physiologic as well as pathologic conditions. There may be other factors whose importance has not yet been ascertained, and it will therefore be easily understood that the interpretation of changes in the cholesterol value of the blood is fraught with difficulties. At present only deductions based on unusually high or unusually low, on markedly progressive or markedly recurrent, cholesterol values can be expected to give any definite clue concerning the actual relation between a disturbance of the cholesterol balance and the associated pathologic symptoms.

The object of my experimental work is to produce malignant proliferation in animals by disturbing the cholesterol balance. For this purpose cholesterol feeding has been used. In some cases roentgen treatment has been employed in addition, to break down the "lymphoid defense" of the animal (Murphy and Morton[23]). Cholesterol tests of the blood were made, not as an end in themselves, but as a means by which the progress of the metabolic disturbance might be gauged. A few observations made during the course of the experiment seem to furnish data concerning some of the factors that influence the cholesterol content of the blood. These observations I wish to present here although the experiment under discussion is not yet completed.

Rothschild,[7] in his studies on the cholesterol content of the blood of rabbits, found that normal animals appear to have an "individual cholesterol standard" to which they adhere with only slight variations. Bloor[24] has observed that in dogs the process of digestion and the chemical constituents of certain types of food do not influence the cholesterol

percentage to any considerable extent.   In the main, this may also be
applied to goats (Table 1, Fig. 298).

TABLE 1.—CHOLESTEROL VALUES IN THE BLOOD OF NORMAL GOATS.
TESTS MADE EVERY TWO HOURS (8 A. M. TO 6 P. M.)
RESULTS EXPRESSED IN PER CENT.

TIME	READINGS*	HIGHEST VALUE
	Goat 21 (male; received cholesterol only).	
8 A. M.	0.216 - - 0.216 - - 0.272† - (0.216)‡	0.272
10 A. M.	0.186 - - 0.216 - - 0.254 - - 0.254 - - 0.266† - - - - - (0.230)	0.266
12 M.	0.242 - - 0.242 - - 0.262 - - 0.262 - - 0.266† - - - - - - (0.216)	0.266
2 P. M.	0.254 - - 0.254 - - 0.266† - - - - - - (0.224)	0.266
4 P. M.	0.216 - - 0.216 - - 0.242 - - 0.242 - - 0.272† - - - - - (0.242)	0.272
6 P. M.	0.210 - - 0.210 - - 0.242 - - 0.242 - - 0.260† - - - - (0.220)	0.260
	Goat 10 (male; normal control).	
8 A. M.	0.158 - - 0.158 - - 0.180 - - 0.180 - - 0.202† - - - - - - (0.168)	0.202
10 A. M.	0.146 - - 0.146 - - 0.186† - - - - - - - (0.158)	0.186
12 M.	0.158 - - 0.158 - - 0.186† - - - - - - - (0.158)	0.186
2 P. M.	0.168 - - 0.168 - - 0.190 - - 0.190 - - 0.202† - - - - - - (0.158)	0.202
4 P. M.	0.186 - - 0.186 - - 0.202† - - - - - - (0.168)	0.202
6 P. M.§	0.130 - - 0.130 - - 0.186† - - - - - - - (0.146)	0.186

* The readings made at each two-hour period were repeated at intervals of two
minutes.

† Value remained constant for four or more readings.

‡ The small dashes represent approximately the number of minutes that elapsed
between the last constant reading and the first reading lower. Note that this interval was
longer for Goat 10 than for Goat 21.

§ The slightly lower values at this time may have been due to the fact that a few clots .
had formed.
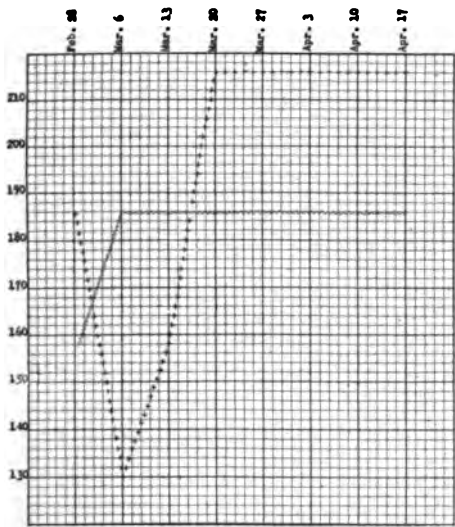
Fig. 298.—Cholesterol values in the blood of two normal goats; Goat 10, male, ∿∿∿∿∿∿; Goat 35,
female, +++.   Note that the values for Goat 10 remained constant for seven weeks and those for Goat 35
remained constant for five weeks.

'16—43

Fig. 298 shows the cholesterol values found in the blood of two normal goats, one male (G10) and one female (G35), during a period of eight weeks (weekly tests). Whereas the values of the male animal remained unchanged for seven consecutive weeks, a drop occurred in the cholesterol value of the female between March 6 and 13, the animal being in heat at the time. The fact that a lower cholesterol value was observed while the animal was in heat indicates that the cholesterol content of the blood is influenced by reproductive activity, an observation to be discussed at greater length in connection with the period following castration.

Table 1 gives the cholesterol values found by tests made every two hours from 8 A. M. to 6 P. M. The effect of the various stages of digestion, even in a ruminating animal, should be clearly demonstrable by an experiment extending over a period of ten hours. Whether the slight variations that occurred are really due to the digestive process is a difficult matter to decide, since a goat ruminates and digests without interruption so that even if food were kept out of its reach for some time the digestive factor could not be entirely eliminated. (Starvation increases the cholesterol content, as Rothschild has ascertained. However, it would seem practically impossible to regulate the food supply for a ruminating animal so that digestion would cease without risking the occurrence of slight symptoms of starvation.) Whether the fluctuations of the cholesterol content (Table 1) are due to the process of digestion or to a greater amount of muscular activity on the part of the animal, they are in themselves so slight that they can hardly be considered significant.

Method of Investigation.—In my experiment the cholesterol content of the blood of six goats was determined every week in the course of seven months. For obvious reasons this part of the experiment is divided into three periods: (1) Observation and cholesterol feeding alone (Fig. 299). (2) Continued cholesterol feeding alone, roentgen treatment alone, and cholesterol feeding combined with roentgen treatment (Figs. 300, 301, and 302). (3) Following castration, other experimental factors unchanged (Figs. 304, 305, and 306).

Period I.—During the first five weeks all the goats were kept under good laboratory conditions and were not subjected to any experiment except that 3 c.c. of blood were taken from the jugular vein by means of a hypodermic syringe every week in order to determine the average cholesterol value of the blood of each animal. At the end of

three weeks all the animals developed symptoms of mange.   The disease remained confined to small areas on the ears or nose, and apparently cleared up in a fortnight.   The changes occurring in the cholesterol value from October 7 to November 1 may be partly accounted for by this infection, and partly by the fact that the goats, having been on
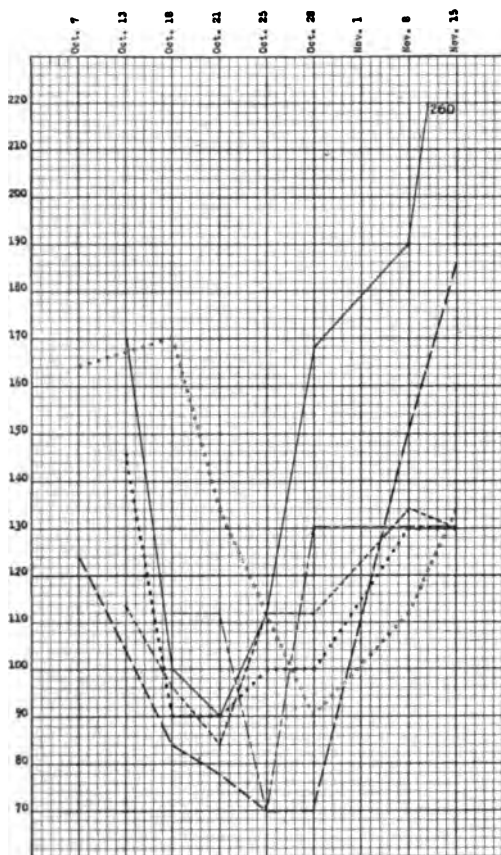
Fig. 299.—Cholesterol values for Period I.   Goat 16, ° ° °; Goat 17, — · —; Goat 19, ———; Goat 20, — — —; Goat 21, — — — —; Goat 26, ...   Note the drop in the values for all the goats during infection (mange) and the increase in the values for Goats 19 and 21 on cholesterol feeding.

free range, had not yet become acclimated to laboratory conditions and stable food.   On November 1 two of the animals (G19 and G21) were fed daily 0.30 gm. of cholesterol in capsules, that the effect of this substance on the cholesterol content of the blood might be studied.   The extraordinary digestive powers of the goat which cause this animal to thrive on the most indigestible articles seemed to justify the apprehen-

sion that the cholesterol might be eliminated without any apparent effect. However, as may be noted from Fig. 299, anxiety on this point proved without foundation, for whereas two of the controls (G16 and G26) did not make up the deficit in their cholesterol value, and the other two (G17 and G20) exceeded their original percentage by a small margin only (0.006–0.018), the two cholesterol-fed animals (G19 and G21) gained
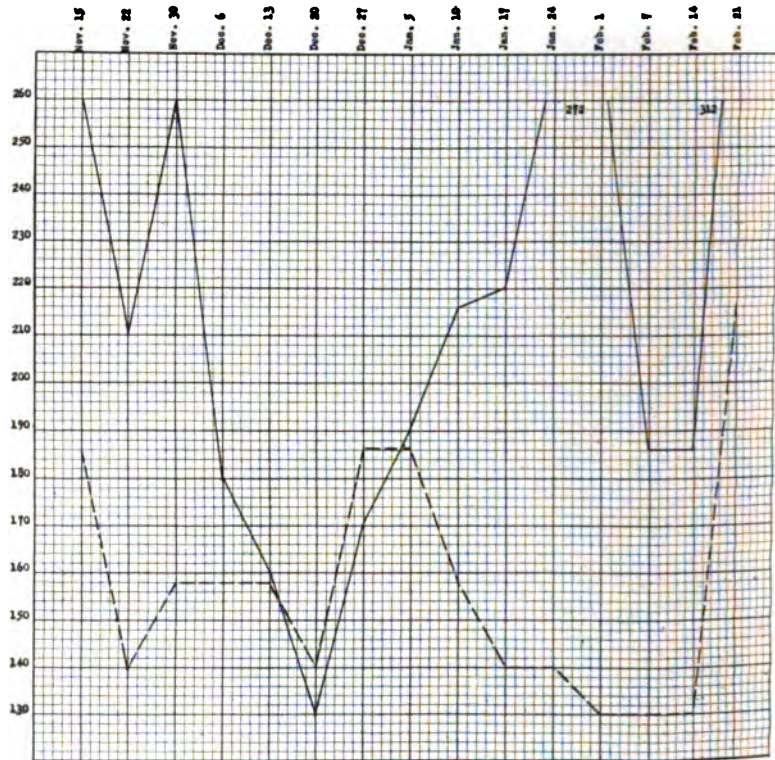
Fig. 300.—Cholesterol values for Group A, Period II. The effect of cholesterol feeding and mange. Goat 19 ————; Goat 21, — — —.

0.90 per cent.; that is, the cholesterol content of the blood increased by 0.090 and 0.062 mgm. respectively, as compared with the original values. Therefore, from Fig. 299, the following conclusions may be drawn:

1. The cholesterol content can be increased in the blood of goats by cholesterol feeding.

2. Parasitic infection (mange) apparently decreases the cholesterol value of the blood. This deduction has been justified by later observa-

tions during a recurrence of mange after the animals had become thoroughly acclimated to laboratory conditions and were steadily putting on weight. The fact may perhaps be explained as the result of an effort on the part of the organism to combat the infection.

Period II.—During the second period observations were made on the effect of cholesterol feeding alone, of roentgen treatment alone,
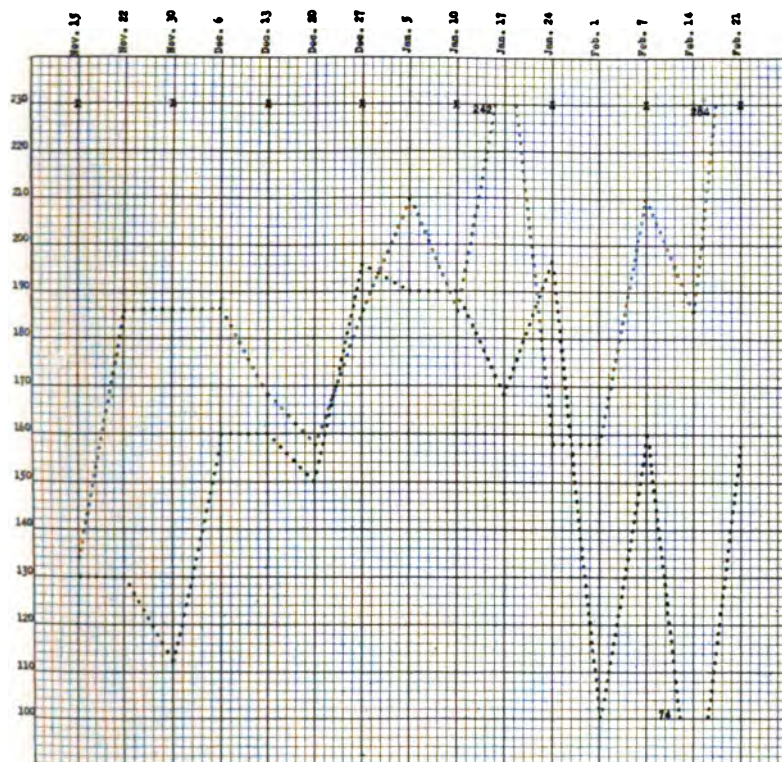
Fig. 301.—Cholesterol values for Group B, Period II. The effect of roentgen-ray treatment and mange. Goat 16, ° ° °; Goat 26 .... X indicates roentgen-ray treatment.

and of roentgen treatment combined with cholesterol feeding, the six goats being divided into three corresponding groups; viz., G19 and G21 (Group A) continued to get 0.30 gm. of cholesterol daily in capsules; G16 and G26 (Group B) diffuse roentgen treatment (diaphragm wide open), consisting of a 12.5 milliamperes per minute dose daily for seven days (2.5 milliamperes at a distance of 24 inches from the tube, exposure five minutes), followed by seven days' rest; G17 and G20 (Group C)

were given the same roentgen treatment but received in addition 0.30 gm. of cholesterol daily without interruption (Figs. 300, 301, and 302).

The interpretation of the results obtained during this period is extremely difficult owing to the number of intercurrent factors, the effect of which on the cholesterol content of the blood can be merely guessed,

Fig. 302.—Cholesterol values for Group C, Period II. The effect of roentgen-ray treatment and cholesterol feeding combined (in the values for Goat 17, the additional influence of pregnancy). Goat 17, — · —; Goat 20, — — —. X indicates roentgen-ray treatment.

since at present data for comparison are not available and can be obtained only by further investigations. On the other hand, the conclusions which seemed warranted by my observations during the first period, viz., the increase of the cholesterol value by cholesterol feeding and the decrease of the cholesterol value by mange, appear to be corroborated.

Thus, G19 (Group A), which already had the highest cholesterol

values during the previous period, will again be found to have higher values than any of the other animals, and G21, which, although it had responded to the cholesterol feeding previously, had done so to a lesser degree, again shows a general increase in the cholesterol content of its blood, less marked than the increase found in the other animal of the same group. Close examination of the curves in Figs. 300, 301, and 302 reveals the influence of the intercurrent factors referred to above. Thus, in the case of G19, a severe recurrence of mange on the shoulder explains the drop of the cholesterol value on November 22. It will be seen that the value went up with the disappearance of the mange. Moreover, the cholesterol dropped again during the following weeks, a decrease that may be partly accounted for by another recurrence of the mange. All the goats except G16 and G20 were affected. In the case of G19, another factor which undoubtedly influenced the cholesterol content from December 13 onward must be considered; viz., the formation of a cyst-like swelling which had become large enough to be noticeable on December 30. This swelling was located near the right nostril, extended over the upper lip, and measured about 2 cm. in diameter. Slight fluctuation was present at first, suggesting that it might be an abscess. The fluctuation then disappeared, and the swelling assumed a tumor-like aspect. To ascertain the exact nature of the tumor it was lanced on January 17 and found to contain pus. A small quantity (1.2 gm.) of the pus was taken for chemical analysis, and the remainder left to be re-absorbed by the animal. A test of the pus for cholesterol showed the cholesterol value to be ten times that of the blood and seemed to warrant the assumption that the abscess was a "deposit" for the increasing surplus cholesterol in the blood. This supposition appeared to be corroborated by the increase of the cholesterol value in the blood during the following weeks, when the remainder of the abscess was being slowly re-absorbed. Several tests made with pus from patients did not give any higher cholesterol values than are usually found in the blood under conditions of slight inflammation. The fluctuations in the cholesterol value of the blood of G21 would appear to be due to the appearance and disappearance of mange.

For the changes in the cholesterol values observed in all of the animals between February 1 and 21 no apparent reason can be found unless extreme changes in the temperature (days on which the thermometer registered 25° to 40° below zero, alternating with days of warm, spring-

like weather) are to be taken into account.*   It is quite conceivable that similar extremes of heat and cold cannot be without effect on general metabolism.

The result of the roentgen treatment (Group B) is not sufficiently striking to permit of any definite conclusions. The fact that a slight drop in the cholesterol value occurs in several instances toward the end of the second period after a week of roentgen treatment (January 24 to February 21, G16, G17, G20, and G26) and is followed by a slight increase after a week of rest, suggests the possibility that the roentgen ray may have a depressing effect on the cholesterol value in the blood. Similar changes were found to occur during the third period. The present data are still too meager to furnish any conclusive evidence although they appear to be in accordance with Soper's[25] observations on the effect of mesothorium rays on the cholesterol value in the blood of rabbits. Soper reports a decrease of the cholesterol content in his animals after mesothorium treatment, but considers it too slight to be significant since it was not corroborated by histologic changes in the spleen. The short duration of his experiment (nine to eleven days) and the fact that several organs play a part in the regulation of cholesterol metabolism might explain his results. If, however, the reduction of the cholesterol content by roentgen rays should become more marked in the course of my experiments or be confirmed by independent studies, it might furnish valuable information concerning the beneficial effect of the roentgen rays on malignant conditions, since the stimulating effect of cholesterol on cell proliferation demonstrated experimentally, and the high cholesterol values found in the blood of a number of cancer patients, seem to indicate that there may be a close connection between disturbances of cholesterol metabolism and malignant growth.

The possible effect of extreme and sudden changes of temperature on the cholesterol content of the blood has been mentioned in the discussion of Group A.

In Group B the influence of mange on the cholesterol values is but faintly indicated. G26 alone had a slight recurrence, and it is difficult to decide whether the drop from 0.160 to 0.150 per cent. (December 13 to 20) is to be attributed to the disease or to the roentgen treatment. On January 10 G16 developed about half a dozen small abscesses in the

* Though the animals were kept in stalls, warmed by the central heating system, there was an outside run in which they spent a great part of the day, apparently by preference.

inguinal region, none of which were larger than a pea. These abscesses cleared up without treatment and on February 7 had completely disappeared. As the pustules were too small to permit the taking of any pus for chemical analysis, it is impossible to say whether their absorption could have caused the changes found in the cholesterol value on January 10 and 17, or were in any way comparable to the abscess on the nose of G19.

By combining roentgen treatment with cholesterol feeding (Group C) I hoped to ascertain which of the two forms of treatment exerted the greater influence on the cholesterol content of the blood. The time allowed for this part of the experiment, four months, seemed amply sufficient to warrant definite results. However, the cholesterol values registered do not furnish conclusive data, although they suggest that roentgen treatment and cholesterol feeding may have neutralized each other; subsequent investigations will have to settle this point. In regard to parasitic infection, a slight recurrence of mange (G17, December 13 to 20) appears to corroborate my previous findings, but another factor will also have to be considered; viz., the influence of pregnancy in combination with roentgen treatment and cholesterol feeding. This will be discussed briefly in connection with Period III.

Summarizing briefly the foregoing:

1. The increase in the cholesterol value of the blood resulting from cholesterol feeding and the decrease resulting from mange observed in the first period have been confirmed by the findings in Period II.

2. The effect of the roentgen rays cannot yet be determined definitely owing to the influence of intercurrent factors; the results suggest the possibility of a decrease of cholesterol values in the blood due to roentgen treatment.

3. The effect of combined roentgen treatment and cholesterol feeding suggests that these factors may neutralize each other, but the influence of intercurrent factors makes definite conclusions premature, and emphasizes the need of further investigations.

Period III.—During this period the effect of castration was studied as an additional factor. The measure was suggested by the influence on malignant conditions of the "cancer age," viz., the age at which reproductive activity decreases. It will be remembered that the principal aim of the experiment was the reproduction of malignant proliferation. One goat of each one of the three groups referred to in the discussion of Period II was castrated. Thus, in Group A (cholesterol feeding alone)

G19 was castrated, and both goats belonging to this group continued
to be fed 0.30 gm. of cholesterol daily; in Group B, G16 was castrated,
and both animals belonging to this group (G16 and G26) continued to
be treated with the same doses of roentgen rays; in Group C, the male
(G20) was castrated, and the combination of roentgen treatment and
cholesterol feeding was continued as before.

In order to verify previous observations on the changes in the cho-
lesterol content caused by anesthesia, samples of the blood were taken
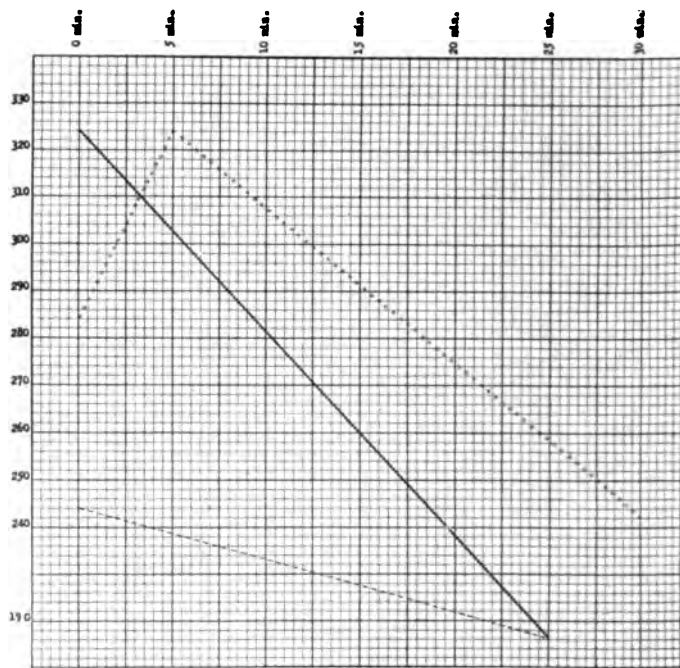
Fig. 303.—The effect of anesthesia on cholesterol values   Goat 16, ° ° °; Goat 19, ————; Goat 20, — — —.

from ten to fifteen minutes after the goats had been given ¼ grain of
morphin, before the administration of the anesthetic, and again on com-
pletion of the operation when the animal was still in narcosis.   In every
instance there was a decrease in the cholesterol content below the value
obtained before the anesthetic was given and similar to the decrease ob-
served in dogs (Fig. 303).   An additional test was made with the blood
of G16, taken five minutes after the beginning of anesthesia (the animal
being completely unconscious) and demonstrated the fact, observed also

in experiments on dogs, that anesthesia is at first accompanied by an increase of the cholesterol content, but that lower values occur after the anesthetic has been given for some time.   The length of this period appears to vary in different animals.   Experiments on the effect of anes-
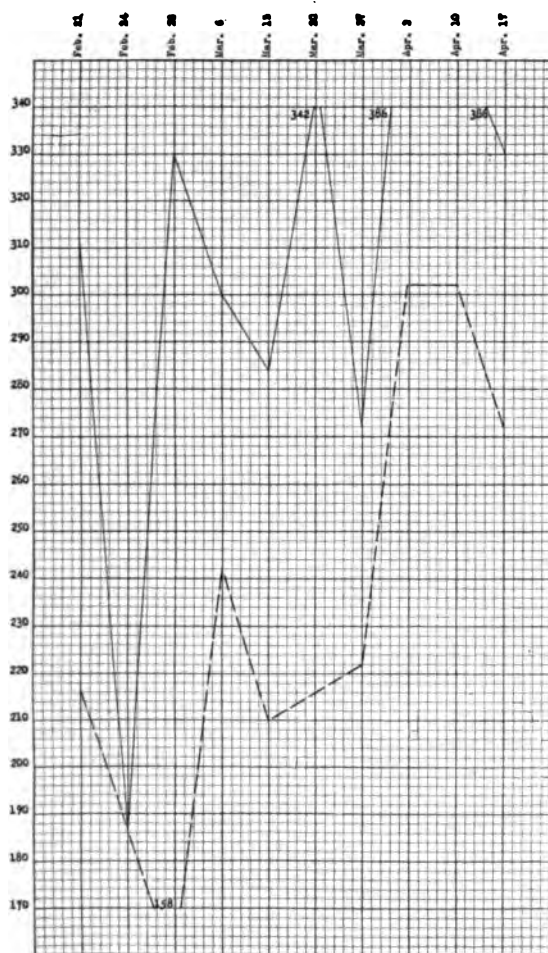
Fig. 304.—Cholesterol values for Group A, Period III.   The effect of cholesterol feeding (Goat 21, — — — —) and of cholesterol feeding and castration (Goat 19, ———).

thesia on the cholesterol content of the blood are still in progress.   The influence of the operative procedure itself need not be taken into consideration, since in our experiments on dogs the above results were obtained by means of the anesthesia alone.

The effect of castration is illustrated in Figs. 304, 305, and 306. In Groups A and B increase of the cholesterol content following castration may be observed by comparing the values of the castrated and the non-castrated animal. In Group C the difference is less marked as the inter-
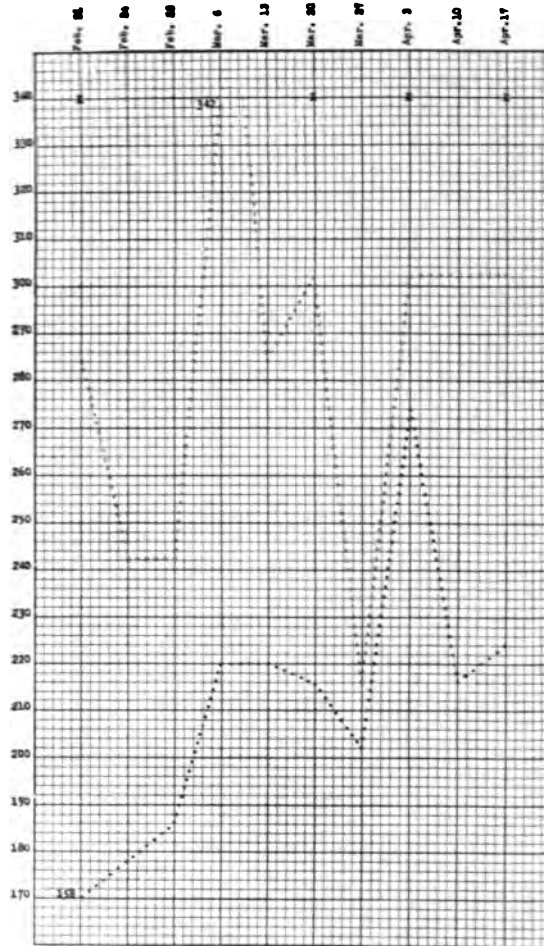
Fig. 305.—Cholesterol values for Group B, Period III. The effect of roentgen-ray treatment (Goat 26, ...) and of roentgen-ray treatment and castration (Goat 16, • • •). X indicates roentgen-ray treatment.

current factor of pregnancy in the animal intended for a control (G17) is likely to have increased the cholesterol values.

During Period III (Figs. 304, 305, and 306) the highest cholesterol values of all were found in the blood of G19 (cholesterol-fed and cas-

trated), the lowest values were found in the blood of G26 (no castration, roentgen treatment only), while intermediate values could be observed in the blood of G16 (roentgen treatment and castration).

It is further interesting to note that although the cholesterol value
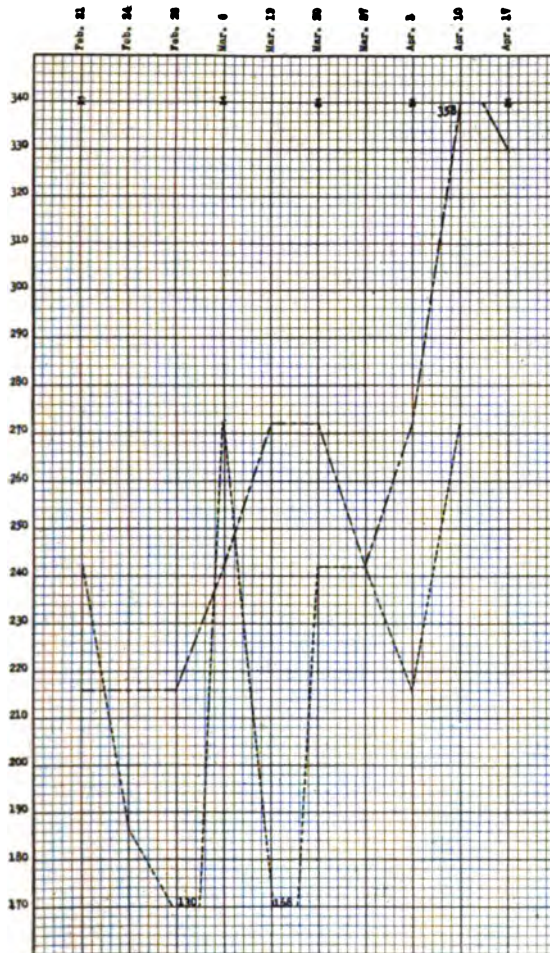
Fig. 306.—Cholesterol values for Group C, Period III.   The effect of cholesterol feeding, roentgen-ray treatment, and pregnancy (Goat 17, — · —) and of cholesterol feeding, roentgen-ray treatment, and castration (Goat 20, — — —).   X indicates roentgen-ray treatment.

of G19 dropped as low as that of G20 (0.186 per cent.) after anesthesia, the animal receiving cholesterol only went up to 0.330 per cent. during the week following operation, whereas G20 which received cholesterol in combination with roentgen treatment went down to 0.130 per cent.

These observations seem to suggest that castration and cholesterol feeding both tend to increase the cholesterol content of the blood, but the roentgen rays, as has already been suggested, appear to have a depressing influence on the cholesterol values, the latter deduction being corroborated by the alternating effect of the week of roentgen treatment (decrease) and the week of rest (increase) which became more marked during this period.

The fact that G26, receiving roentgen treatment alone and having the lowest cholesterol value of all, appears to be slowly increasing his cholesterol percentage may perhaps be explained as follows: It is well known that the reproductive cells in the sex glands are particularly sensitive to the roentgen rays and that animals can be castrated by roentgen treatment alone. Prolonged exposure to the rays, even when extremely small doses are used, may therefore result in permanent injury, if not in the destruction of the reproductive cells.

It is possible that the total number of roentgen-ray units (approximately 150 milliampere minutes of diffuse treatment, wide open diaphragm) which G26 received in five months may have sufficed to produce changes in the sex glands of the animal, and that the increase of the cholesterol values found in its blood are the first indication of these histologic changes. However, microscopic examination of the tissues will have to furnish conclusive evidence on this point.

The sudden drop observed in the cholesterol percentage of G16 on March 27 (from 0.302 to 0.216 per cent.) may have been due to the effect of the roentgen treatment during the week preceding this entry. However, as the animal had been lying down a good deal, appeared listless, and had been feeding badly for three days, the influence of a slight ailment followed by spontaneous and complete recovery must also be considered, especially as the cholesterol values remained constant during the following weeks.

A recent publication by Löwenthal[19] on the effect of castration on the blood of rabbits appears to corroborate my findings as regards the increase of the cholesterol content in the blood of goats.

The effect of pregnancy on the cholesterol values in women has been studied by Neumann and Herrmann,[26] Aschoff,[3] and Autenrieth and Funk.[27] They report that an increase can be demonstrated at the beginning of the fifth month. Bacmeister and Havers[2] observed a similar change in the bile of pregnant bitches. As far as could be ascertained, no other data have been published on the subject.

In my experiment the changes found in the blood of G17 during pregnancy are difficult to account for, because of additional factors (*i. e.*, cholesterol feeding, roentgen treatment). On the whole, the values seem to be slightly higher. That the increase is not more pronounced may be due to the roentgen treatment, to which the organism might be particularly sensitive during pregnancy. As in other instances my observations on this point will have to be verified by future experiments.

In the light of recent studies on the stimulation of cell division by cholesterol, the influence of pregnancy and of castration on the cholesterol content of the blood would seem to be significant; in pregnancy the increase of the cholesterol values might be interpreted as a physiologic measure calculated to stimulate cell division in the embryo, while in castration elimination of the reproductive organs (in which cell proliferation is more constant than in any other part of the body) might be expected to result in a surplus of unused cholesterol.

The results indicated by my observations during Period III may be summarized as follows:

1. Anesthesia appears to reduce the cholesterol content of the blood.

2. Castration tends to increase the cholesterol values; the increase of body fat observed in castrates and the fact that cholesterol is stored in the body fat are in accordance with the apparent effect of castration.

3. The highest cholesterol values were found in the castrated and cholesterol-fed goat, the lowest values in the animal that had not been castrated and had received diffuse roentgen treatment only, while intermediate values occurred in the animal that had been castrated and treated with roentgen rays. These facts seem to support the assumption that castration increases and roentgen treatment tends to reduce the cholesterol content of the blood.

4. The slight but steady increase of cholesterol found in the blood of the goat which received diffuse roentgen treatment alone recalls the fact that the roentgen rays may destroy the reproductive cells to an extent equaling castration, and suggests that the increase itself may be due to the destruction of the reproductive cells in this animal. The observation will have to be corroborated by microscopic findings.

5. The influence of pregnancy on the cholesterol content of the blood, though indicated, is not sufficiently marked to permit definite conclusions. Whereas in the other goats cholesterol feeding and roentgen treatment appeared to neutralize each other, it is possible that preg-

nancy rendered this animal more sensitive to the effect of the rays and that the latter factor preponderated and counteracted the influence of pregnancy. Future observations alone can furnish conclusive data.

TECHNICAL DETAILS CONCERNING THE CHEMICAL ANALYSIS OF THE BLOOD FOR CHOLESTEROL

The original Autenrieth-Funk[27] method was used at first to determine the cholesterol values of the blood in my experiments. Toward the middle of the second period parallel tests were made by Autenrieth's method and Bloor's[24] modification thereof, which was published at the time. Latterly Bloor's first modification has been used exclusively as it is much more simple and in many cases appears to give more accurate results. Bloor's[28] second modification has not been used; the omission of saponification in the latter method gives somewhat higher values, and it was thought advisable to retain one standard in this series of experiments.

The fault of Autenrieth's method, to which Bloor has called attention, the occurrence of a brownish tint in the reaction, making colorimetric comparison difficult, though also observed by me in samples of pathologic human blood, has not given me any trouble in the tests made with goats' blood. In the latter instances both methods gave identical values with only a few exceptions; when a difference occurred it never exceeded 0.025 per cent., and the average values of a great number of readings by both methods have been recorded in the table (Period II, January 17 to February 1).

The test for cholesterol is based on a specific color reaction; on addition of acetic acid anhydrid and sulphuric acid the colorless chloroform extract of the blood assumes a green tone, varying in intensity according to the amount of cholesterol present in the blood. The time required for the reaction, viz., until the maximum color intensity is reached, in any test is fifteen minutes, according to Autenrieth and Funk[27] and Bloor,[24] the reagents being left in the dark at a constant temperature of 35° to 37° C. during that time. In the course of my investigations the following observations led me to modify the factors of time and temperature.

I found that the rapidity of the reaction varied considerably in different blood samples,* the maximum color value being reached much

---

* I tested over 400 different blood samples during the last six months, the cholesterol value being determined in normal human blood, in human blood under various pathologic conditions, and in the blood of several species of experimental animals (dogs, goats, spermophiles). An average of ten readings was made for each test, resulting in a total of 4000 readings.

more quickly in one specimen of blood than in another under parallel conditions. As the exact chemical nature of the process by which the color reaction is caused is not known, the assumption seems warrantable that the presence of other chemical substances besides cholesterol may retard or accelerate the reaction. Every precaution has been taken to prevent recognizable factors (impurity of reagents, difference in temperature) from playing a part in the occurrence of these variations. To obtain data as accurate as possible by taking the occurrence of these variations into account, I have adopted the following procedure:

The test is left in the dark* at room temperature for five minutes only, after which it remains exposed to the light, and readings with the Autenrieth-Hellige colorimeter (control of the instrument with tests containing pure cholesterol) are made at intervals of two minutes until the maximum color intensity is reached. In some cases the maximum value was found after two readings, in others after ten to thirty readings; it remains constant for ten minutes in some and for as long as twenty minutes in others, after which the color begins to fade, giving lower values. It is obvious that a test which reaches its maximum value after two readings or four minutes, and in which the maximum remains constant for eight minutes only, will already have begun to fade when the first reading is made after fifteen minutes, and that, therefore, the value obtained will be lower than would be warranted by the amount of cholesterol present in the blood. When the reaction is of the rapid type described above, it is advisable to make two, three, or even four tests with different portions of the same extract; the same maximum value will be constant for the same length of time in these different portions, and the figures recorded in the tables will represent maximum values which remained constant for at least four consecutive readings at two-minute intervals each.

Another observation which caused me to adopt the above technic was that some tests assume a decidedly yellow-green tint (not the brown tone referred to by Bloor) when left in the dark longer than five minutes. This tint differs materially from the emerald green of the pure cholesterol reaction and makes accurate colorimetric reading difficult. I noticed, however, that the exact shade required for matching the control color (either pure cholesterol or the fluid of the Autenrieth-Hellige colorimeter) can be obtained by exposing yellowish tests to strong daylight (near a window); whereas tests that are slightly too blue-green can be

* I have found an ordinary microscope case very serviceable as a "dark cupboard."

'16—44

corrected by putting them in the dark for a couple of minutes. The actual values are not affected by the change of tint.

DISCUSSION

Although the data furnished by the observations reported in this paper are by no means conclusive, they seem to suggest problems worth studying, viz., the effect of roentgen rays on the cholesterol content of the blood in relation to malignant conditions, the influence of the organs of reproduction on cholesterol metabolism, and the effect of bacterial or parasitic infection. The fact that the primary object of my experiment was the study of possible factors in malignancy rather than the study of cholesterol values for themselves, will, I think, sufficiently explain the indeterminate nature of most of my deductions. It must be remembered also that the animals used for the experiment were young, healthy, and of a species endowed with a remarkable power of resistance and recuperation, having many means of safety at their disposal in the organs that regulate cholesterol metabolism. The adequacy of these organs, moreover, is bound to remain an unknown quantity in every animal as long as the animal is alive. Since, comparatively speaking, the study of cholesterol metabolism is a new field of investigation, data for comparison are scarce, if they are not entirely lacking, as is the case in experimental work of this kind done on goats. However, although my experiment is still in progress, some of the results obtained so far by measures calculated to disturb the cholesterol balance seem to be encouraging, and I hope to publish these shortly.

SUMMARY

1. The average normal cholesterol content of the blood in goats, though not definitely established, appears to be from 0.186 to 0.216 per cent.

2. The cholesterol content of the blood can be increased by cholesterol feeding.

3. Diffuse roentgen treatment appears to lower the cholesterol content of the blood, but conclusive evidence will have to be furnished by future experiments. The beneficial effect of roentgen treatment in malignant conditions, the increase of the cholesterol content observed in the blood of patients suffering from malignant disease, and the stimulation of cell division by cholesterol demonstrated by recent ex-

periments, suggest that the study of the influence of the roentgen rays on the cholesterol content of the blood may be of considerable value.

4. Castration tends to increase the cholesterol values, which may explain the increase of body fat found in castrates and after the cessation of reproductive activity, since the storage of cholesterol in the body fat has been demonstrated.

5. The increase of the cholesterol content of the blood in pregnancy, reported by others, has been found indicated in my experiment, although intercurrent factors forbade definite conclusions.

6. The normal process of growth in the embryo caused by cell proliferation and the effect of cholesterol on cell division referred to above may explain the increase of the cholesterol content of the blood during pregnancy.

REFERENCES

1. Weltmann, O.: "Zur klinischen Bedeutung des Cholesterinnachweises im Blutserum," Wien. klin. Wchnschr., 1913, xxvi, 874–882.
2. Bacmeister and Havers: "Zur Physiologie und Pathologie des Cholesterinstoffwechsels," Deutsch. med. Wchnschr., 1914, xl, 385–388.
3. Aschoff, L.: "Zur Cholesterinesterämie der Schwangeren," Wien. klin. Wchnschr., 1911, xxiv, 559.
4. McNee, J. W.: "Cholesterin; an Account of its Relation to Pathology and Physiology," Quart. Jour. Med., 1914, vii, 221–236.
5. Wacker, L.: "Das Cholesterin und seine Begleitsubstanzen im menschlichen Depotfett beim Carcinom," Ztschr. physiol. Chem., 1912, lxxx, 383–408.
6. Sternberg, H.: "Die Nebenniere bei physiologischer (Schwangerschaft-) und artifizieller Hypercholesterinämie," Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 91–123.
7. Rothschild, M. A.: "Zur Physiologie des Cholesterinstoffwechsels. III," Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 39–64.
8. Stuckey, N. W.: "Ueber die Veränderungen der Kaninchenaorta unter der Wirkung reichlicher tierischer Nahrung," Inaug. Dissert., Petrograd, 1910; Centralbl. allg. Path. u. path. Anat., 1911, xxii, 379.
9. Wesselkin, N. W.: "Ueber die Ablagerung von fettartigen Stoffen in den Organen," Arch. path. Anat., 1913, ccxii, 225–235.
10. Chatalow, S. S.: "Ueber das Verhalten der Leber gegenüber den verschiedenen Arten von Speisfett," Arch. path. Anat., 1912, ccvii, 225–235.
11. Anitschkow, N.: "Die pathologischen Veränderungen innerer Organe bei experimenteller Cholesterinesterverfettung," Deutsch. med. Wchnschr., 1913, xxxix, 741–743.
12. McMeans, J. W.: "Tissue Reactions in Experimental Hypercholesterinemia," Jour. Med. Research, 1916, xxxiii, 481–491.
13. Weltmann, O., and Biach, P.: "Zur Frage der experimentellen Cholesteatose," Ztschr. f. exper. Path. u. Therap., 1913, xiv, 367–378.
14. Anitschkow, N., and Chatalow, S.: "Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse," Centralbl. allg. Path. u. path. Anat., 1913, xxiv, 1–9.
15. Albrecht, H., and Weltmann, O.: "Ueber das Lipoid der Nebennierenrinde," Wien. klin. Wchnschr., 1911, xxiv, 483–484.
16. Stewart: Quoted by McMeans (12).
17. Hueck, W.: "Die Bedeutung der Nebennieren für den Kohlenhydrat- und Cholesterinstoffwechsel," Centralbl. allg. Path. u. path. Anat., 1914, xxv, 397.
18. Gardner, J. A., and Lander, P. E.: "On the Cholesterol Content of the Tissues of Cats Under Various Dietetic Conditions and During Inanition," Biochem. Jour., 1913, vii, 576–595.

19. Löwenthal, K.: "Zur Physiologie des Cholesterinstoffwechsels; Beziehungen zwischen Hoden und Cholesterinstoffwechsel," Beitr. z. path. Anat. u. z. allg. Path., 1916, lxi, 564–569.

20. Rothschild, M. A.: "Zur Physiologie des Cholesterinstoffwechsels: V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand," Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 227–231.

21. Robertson, T. B., and Burnett, T. C.: "The Influence of Lecithin and Cholesterin Upon the Growth of Tumors," Jour. Exper. Med., 1913, xvii, 344–352.

22. Browder, A.: "The Effect of Lecithin and Cholesterol Upon the Division Rate of Paramecium," Univ. California Publications, Physiology, 1915, v, 1–3.

23. Murphy, J. B., and Morton, J. J.: "II. Studies in Lymphoid Activity. The Lymphocyte in Natural and Induced Resistance to Transplanted Cancer," Jour. Exper. Med., 1915, xxii, 204–211.

24. Bloor, W. R.: "Studies on Fat. II. Fat Absorption and the Blood Lipoids," Jour. Biol. Chem., 1915, xxiii, 317–326.

25. Soper, W. B.: "Zur Physiologie des Cholesterinstoffwechsels," Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 232–244.

26. Neumann, J., and Herrmann, E.: "Biologische Studien über die weibliche Keimdrüse," Wien. klin. Wchnschr., 1911, xxiv, 411–417.

27. Autenrieth, W., and Funk, A.: "Ueber kolorimetrische Bestimmungsmethoden: Die Bestimmung des Gesammtcholesterins im Blut und Organen," München. med. Wchnschr., 1913, lx, 1243–1248.

28. Bloor, W. R.: "The Determination of Cholesterol in the Blood," Jour. Biol. Chem., 1916, xxiv, 227–231.

OBSERVATIONS ON CHOLESTEROL RETENTION AS A FACTOR IN CELL-PROLIFERATION *

GEORGINE LUDEN

The influence of heredity, the cancer age, the relatively large percentage of recurrence in malignant conditions, and lesions produced by trauma are recognized by the medical profession throughout the world as important contributory factors in malignant cell-proliferation. It is well known, for example, that in certain persons a slight injury will result in the formation of a rapidly growing tumor—a kick during a football game may be followed by sarcoma,[1] the irritation from the ragged edge of a tooth by inoperable carcinoma. In these cases, however, a mere spark, as it were, causes a conflagration. The injury itself may be considered only a provocative factor, not the real cause, in the formation of the malignant growth; sparks do not create a conflagration unless they fall where inflammable material has accumulated.

That the fundamental factor in malignant diseases, whatever it may be, is widely distributed throughout the organism seems evident from the literature reporting conditions in which more than one tissue has become involved in the process of degeneration. Such cases, although not frequent, are by no means exceptional. Bartlett[2] concludes that "multiple primary malignant tumors occur in approximately 0.2 per cent. of all cases of malignant tumors."

In this connection attention should be drawn to the fact that the term "multiple primary tumors" has been used in the literature repeatedly without distinction for the simultaneous occurrence of (a) different types of carcinoma, (b) carcinoma and sarcoma, and (c) tumors of totally diverse histologic character. The relative frequency of these three varieties of multiple types of malignant growths may be indicated as follows:

1. *Carcinoma Duplex.*—A term originally used by de Vries[3]: Con-

ditions in which two types of carcinoma or carcinoma and epithelioma occur simultaneously.

2. *Carcinoma and Sarcoma.*—Conditions in which malignant degeneration is observed simultaneously in both epithelial and connective tissue.

3. *Multiple Type of Primary Malignant Tumors.*—Conditions in which tumors of a totally diverse histologic character are found simultaneously. These are comparable to those reported by Walter[4] and Hansemann,[5] and are not to be confounded with the class of malignant neoplasms known as teratomas.

As far as can be ascertained, 119 cases of carcinoma duplex, 41 cases of carcinoma and sarcoma, and 15 cases of the multiple type of primary tumors have been observed in man and reported in literature, including the cases reported by Harbitz.[6] In addition I have studied 2 cases of carcinoma duplex, 3 cases of carcinoma and sarcoma, and 2 cases of the true multiple type of neoplasms. One of the latter has been reported previously.

Seven cases of carcinoma and sarcoma in rodents have been reported by Woglom,[8] Haaland,[9] Russell,[10] Loeb,[11] and Nicholson,[12] and 2 cases of the spontaneous multiple type of primary tumors in dogs have been described by Bartlett. It must be especially emphasized that although Bartlett suggests the possibility that the etiology of the types of tumors found in each of his two dogs was different, "one being indirectly due to a metabolic disturbance, the other, the mixed tumor, being in some way connected with an embryonal anlage," none of the primary multiple type of tumors in man herein reviewed belong to the class known as teratomas.

Two other facts demonstrating the ubiquity within the organism of the fundamental factor in malignant cell-proliferation are the occurrence of malignant degeneration in originally benign tumors, commented on by many authorities, and the "precancerous stage" described by Wilson,[13] MacCarty,[14] and others.

As regards the identity of the causative factor, the branches of science that seem most particularly well fitted for the investigation are bacteriology, parasitology, and chemistry. Bacteriology thus far has been unable to furnish any material evidence of bacterial origin of malignancy. Parasitology has yielded many brilliant "finds," none of which has stood a five-year test. Physiologic chemistry, on the other hand, while it has offered no complete explanation of cancer, has already sup-

plied a number of data indicating that marked metabolic changes occur in and go hand in hand with the progress of malignant disease. Lewis and Benedict[15] have called attention to the increase of the sugar content of the blood in carcinoma. Davis[16] describes a hema-urochrom test giving valuable information in cases of malignant disease, which he does not claim to be specific for cancer, but considers indicative rather of an increased hemolysis, cytolysis, and proteolysis. The nitrogen content has been studied by many observers and found increased both in the urine output and in the tumor-tissue (Robin,[17] Mueller, Gaertig, Klemperer, Embden, Knoop, Langenstein[18]). Capella[19] has noted a sulphur reaction positive in the urine of patients with cancer. Pentagna[20] has called attention to the presence and importance of glycogen in malignant tumors "which increases in proportion to the degree of malignancy exhibited by the neoplasm."

It has been universally conceded that normal cell-proliferation or growth is a proliferation of cells within normal bounds, and that a neoplasm represents a form of cell-proliferation exceeding normal bounds. The question then naturally arises: Is there any chemical substance which appears to be essential for normal proliferation, or growth, the activity of which may be traced in abnormal proliferation or malignancy?

The following facts, I believe, seem to indicate that such a substance is cholesterol.

Dorée, Ellis and Gardner[21] have shown by chemical analysis that the cholesterol content of the egg-yolk diminishes proportionally to the growth of the chick embryo, cholesterol being used in the process of cell-proliferation and assimilated in such a way that it cannot be recovered in the same quantity from the mass of cells representing the embryo. Aschoff[22] and Autenrieth and Funk[23] have called attention to the increase of cholesterol in the blood during pregnancy. Bacmeister and Havers[24] demonstrated that, whereas the cholesterol content in the blood of pregnant bitches increases until the pups are littered, it gradually returns to normal shortly afterward. Burnett and Robertson,[25] in experimenting with tumor-grafted rats, showed that the intravenous injection of cholesterol-sodium-oleate emulsion causes the tumors in the injected animals to double in size in a given time those in the tumor-bearing controls, all the animals having been grafted at the same time and with the same tumor. Browder[26] has proved that the addition of 0.01 gm. of cholesterol to the culture-medium increases the rate of di-

vision in paramecia from 1.33 to 5 times, as compared with controls grown in the same culture-medium without added cholesterol.

The above observations strongly suggest the existence of some kind of correlation between cholesterol-increase and cell-proliferation, under both normal and abnormal conditions, and appear to indicate not only that cholesterol is associated with active cell-proliferation, but also that it acts as a stimulant to cell division.

Before enumerating other facts based on experimental and clinical data which seem to support the above deduction concerning the physiologic activity of cholesterol as related to cell-proliferation, a few words may be said in regard to the organs that regulate cholesterol metabolism and its elimination. Named in the order of their apparent relative importance they are as follows:

1. Adrenal (Rothschild,[27] Sternberg,[28] Landau,[29] Gardner and Lander,[30] Stewart,[31] Weltmann,[32] Hueck,[33] McMeans[34]).

2. Liver (Rothschild, Weltmann, Anitschkow and Chatalow,[35] McMeans).

3. Spleen and the "endothelial apparatus" (Aschoff and Landau,[36] Soper,[37] Rothschild, McMeans).

4. Ovary and corpus luteum (McMeans).

Apart from these organs of regulation, the body has at its command a number of other means by which, under normal conditions, it can maintain its cholesterol balance. Surplus cholesterol is eliminated, for example, in the feces (McNee[38]) and the bile (Rothschild), and is stored in both the endothelial lining of the blood-vessels, as in arteriosclerosis (Klotz,[39] Saltykow,[40] Anitschkow, Krylow,[41] McMeans) and in the body-fat (Rothschild, Hueck, Wacker[42]). In addition, there are what might be called "emergency safety valves," such as cholesterol cysts, boils, etc. An instance of the latter occurred in one of our cholesterol-fed goats which developed a boil, the contents of which had a cholesterol value of 0.70 per cent., about four times that of normal goats' blood.

Notwithstanding these natural means of defense against an accumulation of cholesterol, there occur at times symptoms which it seems possible to explain only as being due to cholesterol retention, and these symptoms go hand in hand with cell-proliferation (Figs. 312 and 313).

A patient (No. 63,175), male, aged fifty-seven, came to the Mayo Clinic in 1912 on account of "bladder trouble." On operation (prostatectomy) adenofibromatous hypertrophy was discovered, but no trace of malignancy was noted microscopically. Four years later the man

returned in a critical condition and died within three weeks.   At autopsy
extensive atheromatosis with ulcerating plaques was found in the aorta,

Fig. 307.—(85,046.) Malignant growth involving upper third of ulna and radius—osteochondroma sarcoma. Tumor developed within three months at site of injury sustained two years previously. Showing proliferation of the bone. (Hematoxylin-eosin, × 120.)

Fig 308.—(Same as Fig. 307.) Proliferation of cartilage. (Hematoxylin-eosin, × 250.)
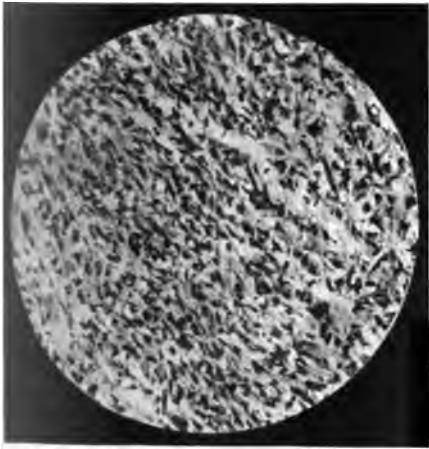
Fig. 309.—(Same as Fig. 307.) Proliferation of connective tissue (Hematoxylin-eosin, × 250.)
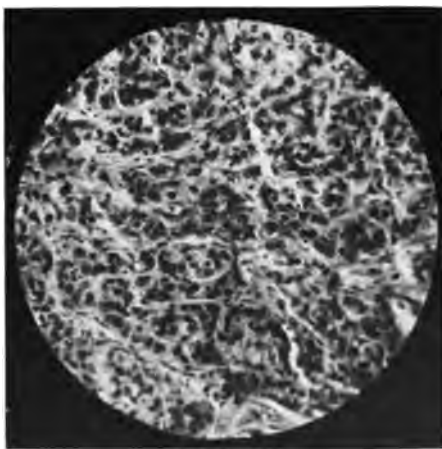
Fig. 310.—(Same as Fig. 307.) Proliferation of epithelium. (Hematoxylin-eosin, × 250.)

together with carcinomatous nodules in the prostatic bed, malignant
proliferation of the epithelium and the sebaceous glands in the supra-
pubic scar.   The skin was not broken.   It will be remembered that arti-

ficial atheromatosis has been produced in animals by prolonged cholesterol feeding (Anitschkow, Saltykow, Stuckey, McMeans) and that the atheromatous plaques were microscopically identical with those found in man.
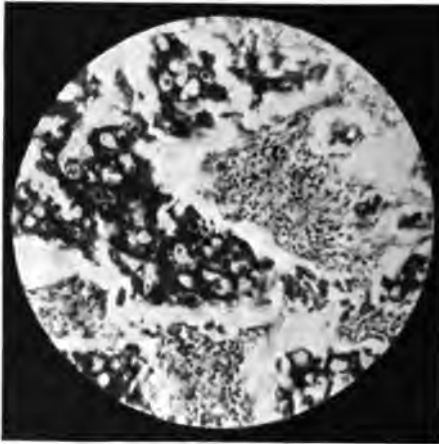
Fig. 311.—(Same as Fig. 307.) Proliferation of the epithelium showing a different type of carcinoma, (myxomatous degeneration) (Hematoxylin-eosin, × 250.)
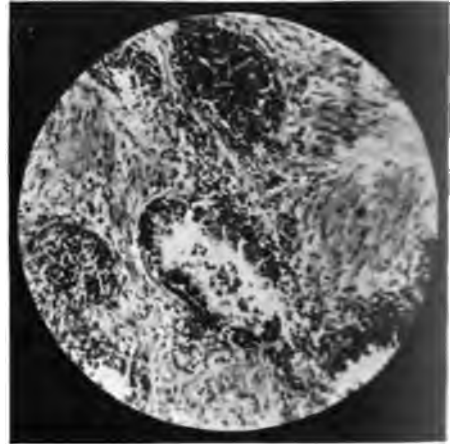
Fig. 312.—(63,175.) Recurrent carcinoma of the prostate. (Hematoxylin-eosin, × 350.)

Fig. 313.—(Same as Fig. 312.) Malignant proliferation of the epithelium and sebaceous glands found at autopsy in operative sinus, four years after operation. (Hematoxylin-eosin, × 350.)

Fig. 314.—(Spermophile 28.) Proliferation of epithelial elements in the bladder of double adrenalectomized spermophile (Citellus tridecemlineatus) which had been given light roentgen treatment (42 Holzknecht in the course of six months at distance of 24 inches from the tube). (Hematoxylin-eosin, × 300.)

Proceeding on the working hypothesis that essential factors for the effectual progress of malignant proliferation are:[43] (1) The creation of a disturbance of metabolism which would lead to an accumulation of cholesterol, (2) an extraneous irritant, and (3) the breaking down of the "lymphoid-defense," the importance of which has been established by the work of Murphy and Morton,[44] I began in March, 1915, to give light treatment of roentgen rays to a double adrenalectomized spermophile (Citellus tridecemlineatus). Experiments conducted by Mann* had already shown that these spermophiles survived double adrenalectomy better than most animals. The results obtained were a marked change in the blood-picture, there being an increase of normoblasts from 0 to 10
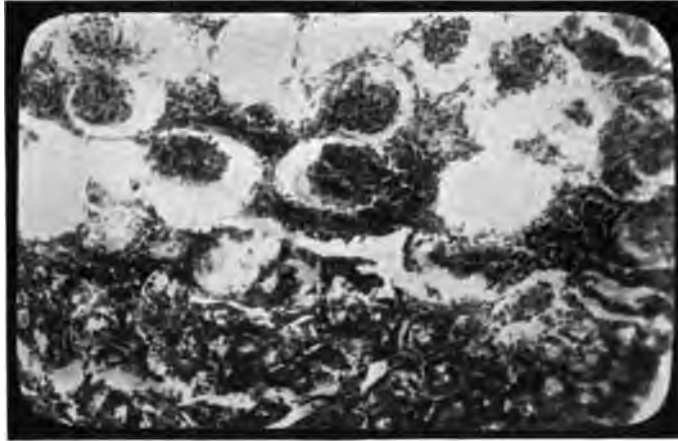
Fig. 315.—(Same as Fig. 314.) Proliferation in the outer zone of the kidney. (Hematoxylin-eosin, × 300.)

per cent. in the course of six months, and the appearance of pathologic, "unripe" leukocytes together with proliferation in various tissues (Figs. 314 and 315). The experiment was then repeated on 8 spermophiles; 2 were double adrenalectomized, 3 were double ovariectomized, and 3 were used as normal controls. The results already described were found to repeat themselves both in blood and tissue. The proliferation of the various types of tissues is comparable to the proliferation of the small arteries in lungs and kidneys together with changes in the spleen resembling those found in "Gaucher's spleen," which have been observed by McMeans after forced cholesterol feeding.

I have studied simultaneously in goats the effect of cholesterol feed-

* Observations to be published.

ing alone, the influence of the roentgen rays alone, and the influence of cholesterol feeding combined with roentgen treatment. Here also similar changes in the blood-picture were observed. Six goats were used for this experiment.

The blood of our six goats was examined weekly for a period of six weeks before the experiments were begun. During this time the animals were kept under uniform and constant conditions, and no great variations in their blood-picture occurred. The most marked changes were those produced by cholesterol feeding alone. These changes in one of the goats (No. 21) are shown in Table 1.

TABLE 1.—CHANGES IN THE BLOOD-PICTURE OF GOAT FED CHOLESTEROL ONLY (GOAT 21)

Results expressed in per cent.

Date, 1915-1916	Polymorphonu-clear Leukocytes	Small Lympho-cytes	Large Lympho-cytes	Eosinophile Leukocytes	Mast Cells	Transitionals*	Neutrophile Myelocytes	Normoblasts	Türk's Irrita-tion Cells	Atypical Small Lymphocytes	Tumor 1†	Tumor 2‡	Cholesterol
				Period 1.—Control Period									
Sept. 10	24	70.5	1.5	..	1.5	..	2	..	..	..	..	..	...
Oct. 4	38	50	7.5	..	1	2	1.5	..	..	..	..	..	0.124
18	30	60.5	7.5	1	1	..	..	..	..	..	..	..	0.084
21	31	58.5	9.5	..	..	..	1	..	..	..	..	..	0.078
25	38	53.5	5.5	..	1	1	1	..	..	..	..	..	0.070
28	54.5	30.5	5.5	2	5	3	..	..	..	..	..	..	0.072
			Period 2.—0.30 Gm. Cholesterol Daily (Beginning November 2)										
Nov. 8	28	25	25	10.5	4	6.5	.5	.5	..	..	..	..	0.150
15	27.5	12.5	10	24	10.5	2	1.5	1	..	..	..	..	0.186
22	26.5	14	10	15	7	2	4	3	.5	6	3	..	0.146
Dec. 6	26.5	9	10	5	5	1·	7	10	1.5	15	5	..	0.158
13	44	2.5	6.5	.5	8	..	11	..	1.5	20	3.5	1.5	0.158
20	33	8	24	2	1	4	11	4	2	12	9	2	0.140
27	30.5	9	13.5	3	3.5	2	8	2	1	18	9	.5	0.186
Jan. 5	25	8	19	2	7	6.5	10	2	..	18	2	1.5	0.168
10	30	5	12.5	3	10	4	12.5	4	..	9	9	1	0.158
17	19	5	11	7	11	16	14	..	.5	15	8	1	0.140
24	27	30	11	5.5	4.5	11.5	2.5	2					0.140
								1 meg.	..	5.5	.5	..	0.140
Feb. 1	38	27	12	4	4.5	8.5	1	..	..	3.5	..	1	0.130
7	30	26.5	16	3	15	3.5	1.5	1.5	..	2.5	..	.5	0.130

Hemoglobin, 20 per cent.; erythrocytes, 16,000,000; leukocytes, 15,200; index, 0.7.

* Transitionals—variety of "large mononuclears," with kidney-shaped nucleus; the typical mononuclears with single round or slightly oval nuclei were not found in this count.

† Tumor 1.—Term borrowed from Schleip's Atlas der Blutkrankheiten, Leukosarcomatosis, p. 128, Fig. 61, with which the cells appeared to be identical.

‡ Tumor 2.—Term borrowed from Schleip's Atlas (Carcinose des Knochenmarks) p. 124, Fig. 59, h., with which cells appeared to be identical.

Recently I have made a series of observations on the cholesterol content of the blood of patients suffering from malignant disease. The Autenrieth-Funk[23] method and Bloor's[45] modification thereof were used. In some cases Bloor's test gave slightly higher values, in others the results were identical. The highest value has been given in the table. The normal cholesterol value as given by Autenrieth and Bloor averages about 0.18 with a low limit of 0.14 per cent. The high normal value has not yet been determined, but I have found it as high as 0.27 per cent. in apparently normal adults. Autenrieth has found a cholesterol value as high as 0.30 per cent. in the blood of normal pregnant women. In a case of xanthoma tuberosum he reports a cholesterol value in the blood of 0.58 per cent. before operation and 0.54 per cent. after operation.

The values found in the blood in the cases of malignancy that I examined are given in Table 2.

TABLE 2.—CHOLESTEROL VALUES IN THE BLOOD OF PATIENTS WITH MALIGNANCY

NUMBER	SEX	AGE; YEARS	CIVIL STATE	DIAGNOSIS	TREATMENT	CHOLESTEROL PER CENT.*
1. 147,020	F	35	M	General carcinomatosis with blood-picture of pernicious anemia	Transfusions; autopsy	0.710
2. 154,152	F	55	M	Epithelioma of tongue	Before treatment†	0.502
3. 136,512	F	39	M	Pernicious anemia (?)	Two transfusions	0.502
4. 152,680	F	52	M	Epithelioma of tongue	Before treatment	0.474
5. 150,864	F	49	M	Mass in the sigmoid (benign?) ‡	Before treatment	0.446
6. 137,213	M	45	M	Recurrent cancer of lower jaw	Before treatment	0.446
7. 150,350	F	48	M	Epithelioma of the arm; amputation§ (exarticulation shoulder)	Radium	0.446
8. 151,635	M	52	M	Cancer (?) of the tongue, blastomycosis	Potassium iodid; iodin locally; radium	0.266
9. 133,093	F	65	M	Multiple lymphomas	Operation; radium; Fowler's solution	0.254

* Average of 10 to 12 readings on each specimen of blood examined.

† Radium appears to lower cholesterol values.

‡ Blood for cholesterol test was taken during anesthesia for operation; patient had been under the anesthetic for fifteen minutes. The effect of ether-anesthesia on cholesterol values is being studied; the values seem to be lowered by anesthesia and by radium treatment.

§ The sigmoid and descending colon appeared to be involved though the character of the tumor could not be defined. Since the patient was in fairly poor health and did not present any clinical symptoms of malignancy, operation which would probably have meant the resection of two-thirds of the large intestine seemed contraindicated. The clinicians expressed the opinion, however, that operation might be necessary eventually on account of obstruction or the development of malignant symptoms.

Weltmann[46] has studied the cholesterol percentages found in the blood under various conditions of disease, and finds them relatively high in arteriosclerosis, nephritis, non-ulcerating tumors, disease of the liver,
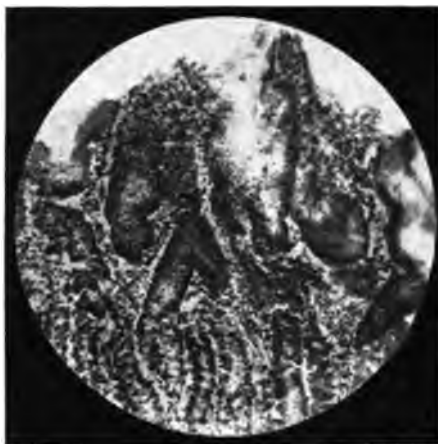
Fig. 316.—(147,420.)   Multiple primary tumors, atypical form of pernicious anemia, high cholesterol value in the blood (0.71 per cent.), malignant proliferation of the gastric mucosa.   (Hematoxylin-eosin × 250.)
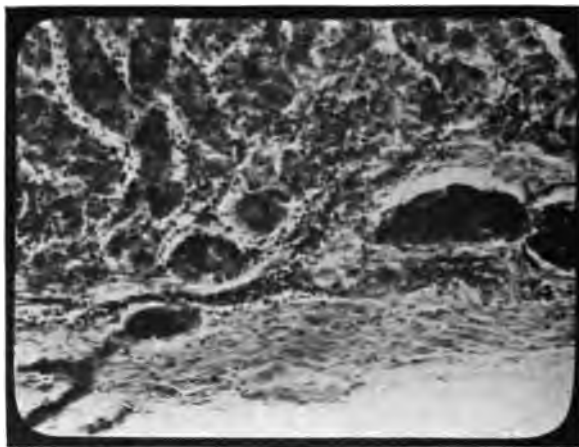
Fig. 317.—(Same as Fig. 316.)   Malignant invasion of the muscularis mucosæ.   (Hematoxylin-eosin, × 350.)

and diabetes, but as he uses another method (a modification of the Neumann-Hermann test with different scale and different color-reaction) and as he himself points out, "obtained not accurate but only comparative values," his data cannot be used for comparison with mine

which are comparable only to Autenrieth's findings in the case of xanthoma tuberosum (0.58) referred to.

As may be seen in Case 147,020 (Table 2), the patient having the highest cholesterol value of all showed not only symptoms of prolifera-
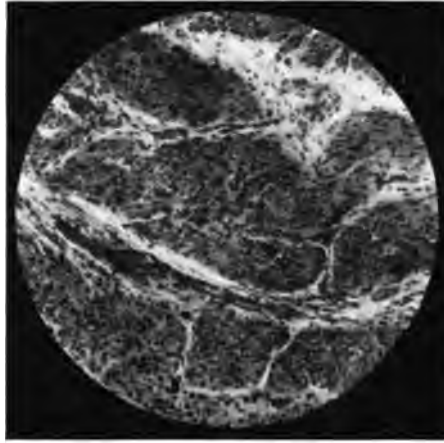
Fig. 318.—(Same as Fig. 316.) Invasion of the outer muscular strata. (Hematoxylin-eosin, X 600
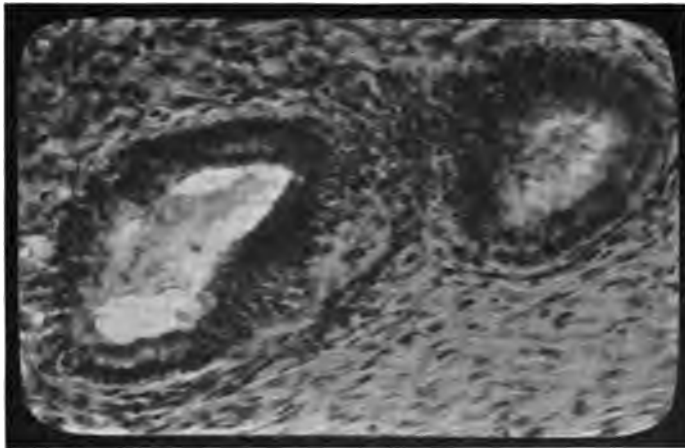
Fig. 319.—(Same as Fig. 316.) Malignant proliferation in the uterine glands (compare with Fig. 312). (Hema-toxylin-eosin, X 600.)

tion in the blood (109 normoblasts, 14 megaloblasts in a count of 300 cells; a picture typical of pernicious anemia according to Ehrlich; atypical according to Grawitz), but malignant degeneration in a number of histologically diverse tissues as well (Figs. 316 to 320).

In Case 140,350 the formation of a rapidly growing, highly malignant tumor was preceded by a clinical history of unrecognized chronic appendicitis. The chronic inflammatory condition had lasted for several
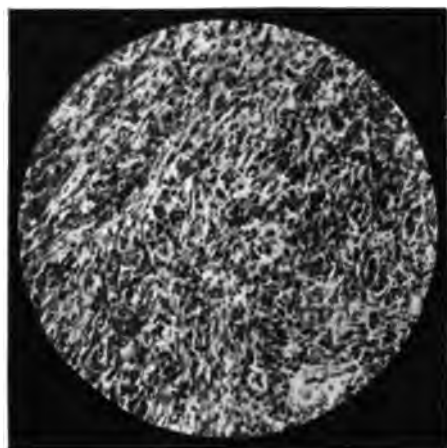
Fig. 320.—(Same as Fig. 316.) Left ovary, tumor 15 cm. diameter. Diffuse type of carcinoma. (Hematoxylin-eosin, × 350.)
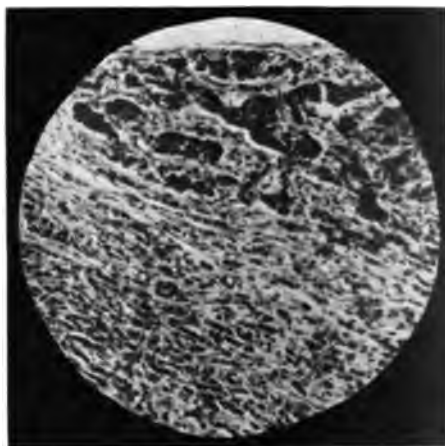
Fig. 321.—(Same as Fig. 316.) Tumor of right ovary, 6 cm. in diameter. Two types of carcinoma. Diffuse type mixed with solid strands. (Hematoxylin-eosin, × 350.)
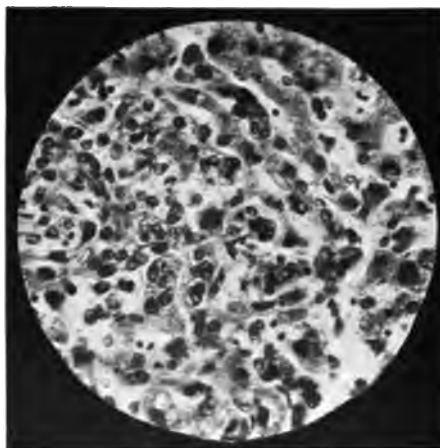
Fig. 322.—(Same as Fig. 316.) Malignant degeneration of the liver "trabecula." This type of malignancy was observed in every section. No metastatic nodules were found. (Hematoxylin-eosin, × 300.)

years, and during this period the patient had gained considerably in weight. At operation uterine fibroids were found. After hysterectomy and unilateral ovariectomy the menstrual period disappeared com-

pletely. A year later slight injury to a birthmark, which had never given any trouble (patient's age, forty-seven), resulted within two months in the development of a highly malignant tumor (Figs. 324 to 326).
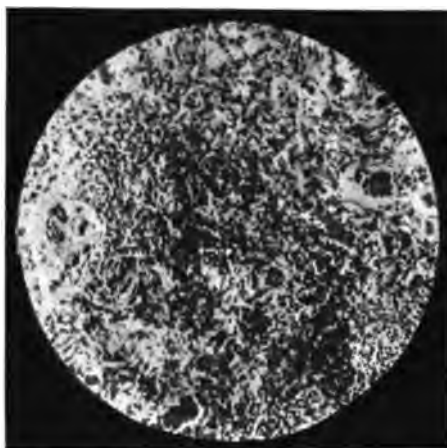
A
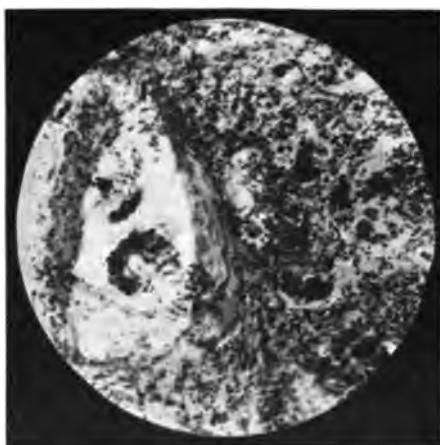
B   *C*

Fig. 323.—(Same as Fig. 316.) Lumbar lymphatic gland containing three different types of carcinoma of metastatic origin (*A*, diffuse; *B*, solid strand; *C*, adenoma). (Hematoxylin-eosin, × 250.)

Five points in the history of this patient seem to deserve special attention: (1) A condition of chronic infection, which, existing during a considerable period, is likely to have overtaxed the adrenal, the chief organ of regulation in cholesterol metabolism; (2) the increase of body-fat

observed in the patient, which must be considered a measure of defense against the accumulation of cholesterol, as has been stated by Rothschild; (3) the high cholesterol value of the blood; (4) the benign tumors found at operation which may be considered another evidence of exist-

Fig. 324.—(150,350.) Melano-epithelioma originating from a birthmark after slight injury.
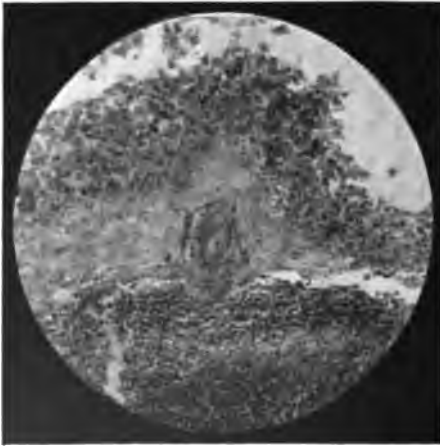
Fig. 325.—(Same as Fig. 324.) Carcinomatous portion of the tumor. (Hematoxylin-eosin, × 350.)
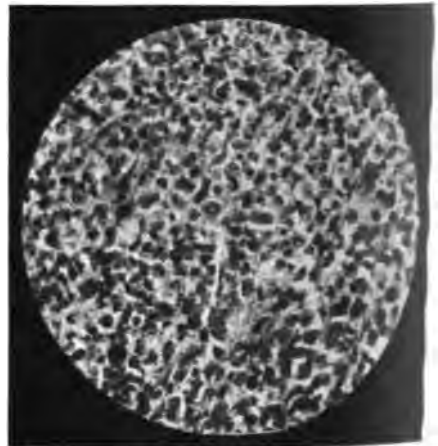
Fig. 326.—(Same as Fig. 324.) Sarcomatous portion of the tumor. (Hematoxylin-eosin, × 800.)

ing hypercholesteremia, and (5) the highly malignant tumor which developed within a year after cessation of the menses and which may be said to suggest that reproductive activity and malignant growth are more closely related than has been universally believed.

The influence of the sex glands on cell proliferation has been studied

by a number of writers (Graf, Almagie, Rohdenburg, Bullock, Johnson, Hilario[47]), the results of these investigations in many cases leading to conclusions diametrically opposed. Sweet, Corson-White and Saxon[48] found that "the receptivity for a tumor with moderate powers of proliferation is increased by castration and that the proliferative power of the neoplasm is augmented." The effect of castration on the formation of benign tumors in the antlers of deer has been commented on by Lauterborn[49] and Tandler and Gross.[50]

Recently Lathrop and Loeb[51] have called attention to the influence of castration in young mice under six months by which the cancer incidence is decreased and the cancer age increased. They mention also "that non-breeding mice become fat at the age of nine months, and at fifteen months almost all are extremely fat—a change usually associated with a decline in the breeding activity." The fact that in these experiments castration exercised a restraining influence on the progress of malignancy only when the operation was performed on young animals seems to suggest that the young organism, not yet entirely grown, might be able to utilize any surplus of cholesterol resulting from castration for purposes of natural growth, or that it has greater powers of elimination at its command. I was able to observe a distinct increase of cholesterol in the blood of goats following castration and the same observation has been made by Löwenthal[52] in rabbits. The increase of body-fat usually observed in castrates and noted by Lathrop and Loeb in their non-breeding mice would seem to indicate (in connection with other evidence concerning the physiologic activity of cholesterol) that the generative organs utilize a certain proportion of the available cholesterol for the formation of the reproductive cells.

SUMMARY

1. Clinical data and experimental observation alike suggest that the causative factor in the production of malignant proliferation is widely distributed within the organism.

2. There is reason to believe that this fundamental factor is chemical in its nature.

3. The existence of a gradual transition between normal, reparative, benign, and malignant proliferation has been commented on by many observers.

4. The evident connection observed between an increase of choles-

terol and proliferation, both normal and abnormal, seems to suggest that cholesterol may act as a stimulant to cell-division.

5. After puberty and under normal conditions the process of cell-division is constantly demonstrable in the sex glands.

6. Recent investigations have shown that the sex glands appear to take an active (perhaps a prominent) part in the regulation of cholesterol metabolism. As cholesterol is stored in considerable quantities in the corpus luteum during pregnancy, and increases in the blood after castration, it seems permissible to assume that it may in some way stimulate the formation of the generative cells.

CONCLUSION

These observations, the fact that the cancer age coincides with the cessation of reproductive activity as shown by the cancer statistics (Prinzing[53]), the importance of metabolism emphasized by Hoffmann in his statistical review on the cancer rates of the Western Hemisphere, and the influence of heredity (the transmission of inadequate organs) established by the work of Slye,[54] all seem to support the view that the retention of cholesterol due to its insufficient conversion or defective elimination may be a primary factor in the etiology of malignant disease.

REFERENCES

1. Coley, W. D.: (Discussion of Elliot, E.: Sarcoma of the Omentum), Ann. Surg., 1910, lii, 401.
2. Bartlett, F. K.: "Multiple Primary Malignant Tumors," Arch. Int. Med., 1914, xiii, 624-639.
3. De Vries, W. M.: "Carcinoma duplex," Zentralbl. f. d. ges. inn. Med. u. d. Grenzgeb., 1912, No. 1. Quoted by Krokiewicz, A.: "Zur Kasuistik multipler, primärer (Multiplicitas diversi generis) maligner Geschwülste," Wien. klin. Wchnschr., 1913, xxvi, 1204-1207.
4. Walter, M.: "Ueber das multiple Auftreten primärer bösartiger Neoplasmen," Arch. klin. Chir., 1896, liii, 1-58.
5. Hansemann, D. P.: "Die mikroskopische Diagnose der bösartigen Geschwülste," Berlin, Hirschwald, 1897. Quoted by Krokiewicz, loc. cit.
6. Harbitz, F.: "Om samtidig forekomst av flere selvstændig voksende—'multiple'—svulster," Norsk Mag. f. Lægevidensk., 1916, lxxvii, Nos. 1-2. Abst. Jour. Amer. Med. Assoc., 1916, lxvi, 994.
7. Luden, G.: "A Case of Supposed Hemachromatosis." Read before Internat. Assoc. Med. Museums, April 1, 1915.
8. Woglom, W. H.: "Carcinosarcoma in the Mouse," Proc. New York Path. Soc., 1914, n. s., xiv, 195-201.
9. Haaland, M.: "Contribution to the Study of the Development of Sarcoma Under Experimental Conditions," Scient. Rep. Imper. Cancer Research Fund, 1908, iii, 175.
10. Russell, B. R. G.: "Sarcoma Development Occurring During the Propagation of a Hemorrhagic Adenocarcinoma of the Mamma of the Mouse," Jour. Path. and Bacteriol., 1910, xiv, 344-378.
11. Loeb, L.: "Ueber Sarkomentwicklung bei einem drüsenartigen Mäusetumor," Berl. klin. Wchnschr., 1906, xliii, 798-802. Also Univ. Pennsylvania Med. Bull., 1906, xix, 113.

12. Nicholson, G. W.: "A Small Carcinoma in Association with a Transplanted Sarcoma in a Rat," Jour. Path. and Bacteriol., 1912, xvi, 518–522.

13. Wilson, L. B., and McDowell, I. E.: "A Further Report of the Pathologic Evidence of the Relationship of Gastric Ulcer and Gastric Carcinoma," Amer. Jour. Med. Sci., 1914, cxlviii, 796–816.

14. MacCarty, W. C.: "Histogenesis of Cancer of the Stomach," Amer. Jour. Med. Sci., 1915, cxlix, 469–476. MacCarty, W. C., and Broders, A. C.: "Chronic Gastric Ulcer and Its Relation to Gastric Carcinoma," Arch. Int. Med., 1914, xiii, 208–210.

15. Benedict, S. R., and Lewis, R. C.: "Sugar Content of the Blood in Cancer," Med. Rec., 1914, lxxxvi, 650.

16. Davis, T. G.: "Hema-uro-chrome: A New Laboratory Test for Cancer and Sarcoma," Amer. Jour. Med. Sci., 1913, cxlv, 857–865.

17. Robin, A.: "L'indosé azoté global, l'azoté ammoniacal, l'amino-acidurie et le coefficient de Maillard dans l'urine des cancéreux," Bull. de l'Assoc. franc. pour l'étude du cancer, 1914, vii, 295–304.

18. Mueller, Gaertig, Klemperer, Embden, Knoop, Langenstein. Quoted by Blumenthal, F.: "Die chemischen Vorgänge bei der Krebskrankheit," Ergeb. d. Physiol., 1910, x, 363–428.

19. Capella, M.: "Del comportamento del solfo orgenico urinario nei tumori maligni," Policlinico, Sez. med., 1914, xxi, 575–580.

20. Pentagna, O.: "Sulla presenza e sul significato del glicogeno nei tumori maligni," Gazz. internaz. di med., 1914, xvii, 649–653.

21. Dorée, C., and Gardner, J. A.: "The Origin and Destiny of Cholesterol in the Animal Organism," Proc. Roy. Soc. London, 1908, s. B., lxxx, 212–239; 1909, lxxxi, 109–132. Fraser, M. T., and Gardner, J. A.: Ibid., 230–247. Ellis, G. W., and Gardner, J. A.: Ibid., 505–515; 1911–1912, lxxxiv, 461–470; 1912, lxxxv, 385–393; 1913, lxxxvi, 13–18. Gardner, J. A., and Lander, P. E.: 1913, ibid., lxxxvi, 229–236.

22. Aschoff, L.: "Zur Cholesterinesterämie der Schwangeren," Wien. klin. Wchnschr., 1911, xxiv, 559.

23. Autenrieth, W., and Funk, A.: "Ueber kolorimetrische Bestimmungsmethoden: Die Bestimmung des Gesamtcholesterine im Blut und in Organen," München. med. Wochenschr., 1913, lx, 1243–1248.

24. Bacmeister and Havers: "Zur Physiologie und Pathologie des Cholesterinstoffwechsels," Deutsch. med. Wchnschr., 1914, xl, 385–388.

25. Robertson, T. B., and Burnett, T. C.: "The Influence of Lecithin and Cholesterin Upon the Growth of Tumors," Jour. Exper. Med., 1913, xvii, 344–352.

26. Browder, A.: "The Effect of Lecithin and Cholesterol Upon the Division Rate of Paramecium," Univ. California Pub. in Physiol., 1915, v, 1–3.

27. Rothschild, M. A.: "Zur Physiologie des Cholesterinstoffwechsels," III. Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 39–64.

28. Sternberg, H.: "Die Nebenniere bei physiologischer (Schwangerschaft-) und artificieller Hypercholesterinämie," Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 91–123.

29. Landau, M., and McNee, J. W.: "Zur Physiologie des Cholesterinstoffwechsels," Beitr. z. path. Anat. u. z. allg. Path., 1914, lviii, 667–699.

30. Gardner, J. A., and Lander, P. E.: "On the Cholesterol Content of the Tissues of Cats Under Various Dietetic Conditions and During Inanition," Biochem. Jour., 1913, vii, 576–595.

31. Stewart: Quoted by McMeans, J. W., loc. cit., p. 488.

32. Weltmann, C.: "Ueber das doppeltbrechende Lipoid der Nebenniere," Beitr. z. path. Anat. u. z. allg. Path., 1913, lvi, 278–324.

33. Hueck, W.: "Die Bedeutung der Nebennieren für den Kohlenhydrat- und Cholesterinstoffwechsel," Centralbl. f. allg. Path. u. path. Anat., 1914, xxv, 397.

34. McMeans, J. W.: "Tissue Reactions in Experimental Hypercholesterinemia," Jour. Med. Research, 1916, xxxiii, 481–491.

35. Anitschkow, N., and Chatalow, S.: "Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse," Centralbl. f. allg. Path. u. path. Anat., 1913, xxiv, 1–9.

36. Aschoff, L.: Verhandl. d. Naturf. Gesellsch., 1913, xx. Landau: Ziegler's Beiträge, 1913, lviii, Deutsch. path. Gesellsch., 1914. Quoted by Soper, loc. cit.

37. Soper, W. B.: "Zur Physiologie des Cholesterinstoffwechsels," Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 232–244.

38. McNee, J. W.: "Cholesterin: An Account of its Relations to Pathology and Physiology," Quart. Jour. Med., 1914, vii, 221–236.

39. Klotz, O., and Bothwell, M. E.: "Inhibition of Sodium Oleate Hemolysis and Toxicity by Cholesterin," Proc. Soc. Exper. Biol. and Med., 1915, xii, 199–201.

40. Saltykow, S.: "Experimentelle Atherosklerose," Beitr. z. path. Anat. u. z. allg. Path., 1914, lvii, 415–473.

41. Krylow, D. D.: "Experimentelle Studien über Nebenniererinde," Beitr. z. path. Anat. u. z. allg. Path., 1914, lviii, 434–467.

42. Wacker, L.: "Das Cholesterin und seine Begleitsubstanzen im menschlichen Depotfett beim Carcinom," Zeitschr. f. physiol. Chem., 1912, lxxx, 383–408.

43. Luden, G.: "Studies on a Cell (Zehbe's) Found in Cases of Human Carcinoma," Jour. Cancer Research, 1916, i, 115–116.

44. Murphy, J. B., and Morton, J. J.: "The Lymphocyte in Natural and Induced Resistance to Transplanted Cancer," Jour. Exper. Med., 1915, xxii, 204–211.

45. Bloor, W. R.: "Studies on Blood Fat. II. Fat Absorption and the Blood Lipoids," Jour. Biol. Chem., 1915, xxiii, 317–326.

46. Weltmann, O.: "Zur klinischen Bedeutung des Cholesterinnachweises im Blutserum," Wien. klin. Wchnschr., 1913, xxvi, 874–882.

47. Hilario, J. S.: "Castration Exerts no Influence Upon the Growth of Transplanted or Spontaneous Tumors in Mice and Rats," Jour. Exper. Med., 1915, xxii, 158–173.

48. Sweet, J. E., Corson-White, E. P., and Saxon, G. J.: "The Relation of Diets and Castration to the Transmissible Tumors of Rats and Mice," Jour. Biol. Chem., 1913, xv, 181–191.

49. Lauterborn, R.: "Die Entstehung wuchernder Geschwülste durch Störungen der inneren Sekretion im Bereich des Geschlechtsapparates," Zeitschr. f. Krebsforsch., 1915, xv, 173–183.

50. Tandler and Gross: "Ueber den Einfluss der Kastration auf den Organismus," Wien. klin. Wchnschr., 1907, xx, 1596–1597.

51. Lathrop, A. E. C., and Loeb, L.: "Further Investigations on the Origin of Tumors in Mice," Jour. Cancer Research, 1916, i, 1–19.

52. Löwenthal, K.: "Zur Physiologie des Cholesterinstoffwechsels; Beziehungen zwischen Hoden und Cholesterinstoffwechsel," Beitr. z. path. Anat. u. z. allg. Path., 1916, lxi, 564–569.

53. Prinzing: "Der Krebs in Württemberg und sein Auftreten in krebsarmen und krebsreichen Oberämtern," Zeitschr. f. Krebsforsch., 1914, xiv, 412–490.

54. Slye, M.: "The Incidence and Inheritability of Spontaneous Tumors in Mice," Jour. Med. Research, 1914, xxx, 281–298, and other papers.

THE TRANSFUSION OF BLOOD IN THE TREAT-
MENT OF PERNICIOUS ANEMIA *

ALEXANDER ARCHIBALD

The transfusion of blood for pernicious anemia in our experience has usually been followed by marked benefit to the patient. In some instances one transfusion was sufficient to secure the desired effect, the improvement continuing under subsequent medication. In most instances, however, two or more transfusions were necessary before definite improvement was noted. In only a few were the results of transfusion unsatisfactory, this being due, I think, to the fact that the bone-marrow was in a depleted and deteriorated condition.

When transfusion of blood from one person to another was first introduced, the operation was limited to emergencies in which the patient had lost large amounts of blood as a result of accident or some form of disease. In recent years, however, blood transfusion has become a therapeutic measure and is widely employed in the treatment of various diseases and conditions. Infectious diseases, toxemias, hemophilia, purpura, have all been treated by the transfusion of blood, with more or less gratifying results. Most commonly blood transfusion is employed in the treatment of the various types of anemia, more especially pernicious anemia.

The literature on the subject of blood transfusion is concerned chiefly with the technic and the different methods of operation. Very little has been said regarding the results. Ottenberg and Libman, however, dealt with the subject in detail and reported the results of transfusion in 24 cases of pernicious anemia. They concluded: (1) That blood transfusion did not cure pernicious anemia, but was of great benefit in at least one-half of the cases; (2) that patients suffering from the chronic form of the disease were more likely to respond to transfusion than those

who had reached a severe degree of anemia in several months and were evidently suffering from an acute type of the disease; and (3) when one transfusion fails to produce benefit, a second should be tried from another donor.

Twenty-five cases of pernicious anemia were treated by blood transfusion at the Mayo Clinic between the months of March, 1915, and May, 1916, and one was so treated in June, 1913. In the 26 cases 46 transfusions were performed: 11 patients had one transfusion; 12, two; 1, three; 2, four. Of the 26 cases, 15 were males and 11 females. The ages varied between twenty-nine and sixty-nine. One patient was between twenty and thirty, four between thirty and forty, four between forty and fifty, twelve between fifty and sixty, and five between sixty and seventy. Up to the sixth decade, the age of the patient, other conditions being equal, had no effect on the result of transfusion. Of the five patients over sixty, however, only one showed definite improvement. The spleen was removed from 12 of the 26 patients, this operation being performed on selected cases. In the total number, therefore, we are able to study only the immediate results of blood transfusion. The later results of the fourteen non-splenectomized cases will be studied independently. The majority of the 26 cases presented a picture of marked debility and anemia.

With regard to the relationship of the duration of symptoms and the number of attacks to the results of treatment by transfusion, it is difficult to arrive at definite conclusions. The longest history extended over a period of six years and the shortest over a period of three months, the average duration of symptoms being 1.8 years. Patients who gave a history of definite remissions, even though their illness had existed several years, apparently received the most benefit from transfusion. A second group having a more or less prolonged history without remissions often failed to respond. A third group who gave a history of a duration of symptoms for a period of a few months and presented a clinical picture of an acute form of the disease was usually little affected by transfusion. In this group there were four. In only one was transfusion followed by satisfactory results. The donors in these cases were usually relatives or friends of the patients, so that a direct test was done for each. The results following the transfusion of the blood of relatives were not superior in any way to those following transfusion from donors not related. In fact, a few patients who received no benefit from the blood of relatives were later greatly improved by transfusion from a friend. According

to Ottenberg and Libman,* a different donor should always be tried if the first transfusion fails to improve the condition of the patient. When two or more transfusions were necessary, one was usually given each week. This allowed sufficient time to study the changes in the blood and the effects on the general condition of the patient. As a rule, we transfused comparatively large amounts of blood (500 c.c.) from donor to recipient at each transfusion. Satisfactory results have been obtained by others by transfusing small amounts at short intervals. One of our patients received only 50 c.c. of blood during a crisis and the hemoglobin rose from 24 per cent. to 64 per cent. in twenty-three days. Another patient, also in a critical condition (hemoglobin, 23 per cent.), received 90 c.c. at each of two transfusions. There was no improvement following the transfusion, and, while the patient lived for six months, at no time was there a remission of symptoms.

In only one of our cases was there a severe reaction following transfusion. Two transfusions were done for this patient, the wife being the donor at the first, and a friend at the second. After both transfusions the patient had a mild grade of fever and a severe chill lasting forty minutes. Following the first transfusion there was also hemoglobinuria. This patient received no benefit whatever from the transfusions, and we were unable to account for the severe reaction. Thirteen of the patients had no reaction. In one case the record was lost. The remaining 11 patients had a mild degree of fever for a day or two, 4 of them experiencing a slight chilly sensation. It has been noted by others that patients having a mild reaction following transfusion usually receive the most benefit, but in our cases I was unable to confirm this observation.

In judging the results of treatment by transfusion we relied mainly on the changes in the blood-picture. A complete count was usually made once every week, and when it was considered necessary, a partial count was made in the interval. The behavior of the hemoglobin and the erythrocytes is perhaps most important. We feel, however, that the number of leukocytes and the nature of the differential count should be considered. As a general rule, severe cases of pernicious anemia or cases of long duration have a leukopenia. The differential count shows a low relative and absolute percentage of polymorphonuclear neutrophils and a high relative and absolute percentage of small lymphocytes. A blood-count of this kind probably indicates a degeneration of the bone-marrow.

* Ottenberg, R., and Libman, E.: "Blood Transfusion, Indications, Results, General Management," Amer. Jour. Med. Sci., 1915, cl, 36–69.

With regard to the changes of the leukocyte count following transfusion, no definite conclusions could be reached. As a rule, the nature of the differential count was not affected.

Following splenectomy in such cases, however, the leukocytes increase in number and the differential count becomes more nearly normal, indicating that in some way the bone-marrow is stimulated to activity as a result of the removal of the spleen.

Of the 26 cases, 18 showed a marked rise in the percentage of hemoglobin. Ten of these patients required only one transfusion, 6 had two transfusions, 1, three, and 1, four. Twelve of the 18 cases showed at the same time a marked increase in the number of erythrocytes. In the remaining 6 cases there was no appreciable change in the number of red cells. In 9 of the 18 cases the leukocytes were increased in number. In no instance was the nature of the differential count changed, whether or not the relative percentage of polymorphonuclears and lymphocytes was normal or increased. In one case there was only a slight increase in the percentage of hemoglobin and the number of erythrocytes. In 7 cases the blood-picture was not altered in any way by transfusion and the patients' condition either gradually became worse or remained much the same during the period of treatment.

The 18 cases which derived definite benefit from transfusion had an average of 29 per cent. hemoglobin; 3 were below 20 per cent.; 8 between 20 and 30 per cent.; 4 between 30 and 40 per cent., and 3 had 45 per cent., this being the highest percentage in the series. The lowest was 10 per cent. The 7 cases which failed to respond to transfusion had an average of 30 per cent. hemoglobin. In 1 the hemoglobin was 15 per cent.; 2 were between 20 per cent. and 30 per cent.; 3 between 30 and 40 per cent., and 1 had 45 per cent. In this series, therefore, we find that those cases which showed no improvement from transfusion had a higher average percentage of hemoglobin than those in which satisfactory results were obtained. Ottenberg and Libman found that the average percentage of hemoglobin in 14 cases showing a remission following transfusion was 27 per cent., whereas the average of 9 cases showing no remission was 20 per cent.

When treatment is first begun, it is impossible to foretell the result of transfusion in an individual case. In many instances of a severe grade of anemia striking results may follow the procedure. In general, I may say, our results correspond closely to those of Ottenberg and Libman, namely, that the greatest benefit is obtained usually in the chronic cases in which there have been remissions during the course of the disease.

As a rule, the improvement in the general condition ran parallel with the increase in the percentage of hemoglobin. The appetite improved and the patient felt stronger and had a general feeling of well-being, which was notably absent previous to transfusion. In some of the cases in which no change was produced in the blood-picture the patient's general condition was improved temporarily. Numbness, burning, and tingling of the hands and feet are perhaps the most trying and persistent symptoms, and, as would be expected, are only temporarily lessened in degree by blood transfusion.

From these statistics we find that 69 per cent. of the patients received definite benefit from transfusion. In all these patients except three the disease was in the active stage when treatment was begun. Accordingly, there is no doubt that the remission was the result of transfusion. Three of the patients were evidently recovering from a crisis at the time treatment was instituted, and in each instance transfusion was followed by more rapid and striking results than in patients suffering from the active stage of the disease.

NON-SPLENECTOMIZED PATIENTS

One of the 14 non-splenectomized patients had had a transfusion before removal of the spleen for pernicious anemia was practised at the Mayo Clinic. Thirteen were considered unfavorable cases for splenectomy. Marked cord changes, senility, and independent organic disease of other organs were the chief contraindications.

It would not be right to consider the results of transfusions in this series of 14 cases as indicating probable results in any consecutive series. It is interesting to find, however, that 7 of the 14 patients received marked immediate benefit from transfusion. In 6 instances transfusion failed to benefit and the patients died from a few weeks to a few months afterward. One patient received temporary benefit which lasted only a few months. Of the 6 patients who received no benefit from transfusion, 4 were more than sixty years of age, 1 was fifty-five years, and 1 forty-one years. In 2 of the cases the hemoglobin was between 20 and 30 per cent.; in 1 case, 37 per cent.; and in the remaining 2, 45 per cent. In 5 cases the average duration of symptoms was 21.6 months. The sixth case was of the acute type, and the patient had been ill only 2.5 months. The hemoglobin of this patient previous to transfusion was 28 per cent. Two transfusions were given. Nineteen days after the first transfusion the hemoglobin was 20 per cent. Each transfusion was followed by severe reaction, and the patient refused further treatment.

Of the patients who improved following transfusion, one had the acute type of the condition and gave a history of a duration of symptoms of only six months. This patient was extremely anemic and debilitated, and ran a temperature of 100° to 101° F. The usual medication having been unsuccessful, he was given two transfusions within a week. Seven days previous to transfusion his hemoglobin was 28 per cent. Thirteen days after the first transfusion it was 43 per cent. The fever subsided and the patient felt stronger. This patient is one of our very recent cases, and in all probability splenectomy will be advised later. Of the 6 remaining patients, the average age was fifty-six years, and the average duration of symptoms, 12.3 months. Two had a hemoglobin percentage between 20 and 30, 3 a percentage between 30 and 40, and 1 a percentage of 45. Two of these patients reported themselves in excellent condition five and seven months respectively after transfusion, and one gave a similar report nine months after transfusion. Blood-counts were not obtained. Two patients had a recurrence of symptoms five and nine months after transfusion. One patient was not heard from.

Notwithstanding the fact that these 14 patients were in extremis, 6 of them received immediate benefit from transfusion and in 5 cases a comparatively long remission from symptoms was secured.

CONCLUSIONS

1. Sixty-nine per cent. of the entire series of patients received marked immediate benefit from transfusion. In 50 per cent. of the 14 unfavorable cases the patients showed similar improvement. All except 3 were given the transfusions during the crisis, so that undoubtedly transfusion was the cause of the remissions.

2. In 15 of the 26 cases, 2 or more transfusions were necessary. When no benefit is derived from one transfusion, a different donor should be tried.

3. Chronic cases with a history of remissions are the most likely to respond to transfusion. Other types of pernicious anemia may also respond. It is impossible to foretell the results of transfusion in any individual case.

4. The age of the patient up to the sixth decade has no effect on the results of transfusion.

5. When the blood is properly tested transfusion is practically free from danger. A slight reaction following transfusion is not necessarily indicative of improvement.

A REPORT ON THE TREATMENT OF PERNICIOUS ANEMIA BY TRANSFUSION AND SPLENEC-TOMY *

HERBERT Z. GIFFIN

It is difficult to appreciate the fact that pernicious anemia is at present an incurable and fatal disease which in some respects is more to be dreaded than cancer. Its relapses, remissions, and merciless progressive course impress on us the necessity for a universal study of its manifestations. A thorough trial of splenectomy in the treatment of pernicious anemia is therefore warranted, though a consideration of the results is at present necessarily confused by fallacies and insufficient data. There is so far no evidence that splenectomy has cured pernicious anemia, but there are definite indications of consistent temporary improvement in a majority of instances.

Our early experience with splenectomy for pernicious anemia was discouraging. During the past two years, however, it has become evident that a marked reaction and a consistent temporary gain, at least for a period of months, follows splenectomy in selected cases, and surgical treatment has been more frequently suggested after a frank explanation to the patients concerning the course of the disease, the inadequacy of present methods of treatment, and the experimental nature of the procedure.

In February, 1910, the spleen was removed from a patient (A7040) who suffered from severe attacks of epistaxis and had a very large spleen, an icteroid tinge, and a blood-picture of pernicious anemia, including the presence of megaloblasts. Splenectomy was advised, not with the specific idea of applying that treatment to pernicious anemia, but largely because of the great size of the spleen and the somewhat indefinite characteristics of the clinical features of the case. The patient did not report himself as improved, and died three years after operation with pneumonia.

Experience may show that cases of this type, in which there are a very large spleen, a hemolytic type of anemia, and a blood-picture of pernicious anemia, may better be grouped separately, as suggested by Moffitt,[1] but they cannot at present be omitted from consideration in a study of this character.

The remaining patients of this series were operated on between August 1, 1914, and April 1, 1916. The records extended up to June 1, 1916, from twenty-three months to three months following operation; most of them, however, were for periods of less than one year.

Preoperative Transfusion.—Preoperative transfusion has been done in 19 cases, from one to four transfusions having been given in each instance. A marked gain followed transfusion in 8 cases. Very rapid and decided gains were seen in two patients. In one the hemoglobin rose from 10 to 40 per cent., with a gain of 2,000,000 red cells in one month: in the other the hemoglobin rose from 16 to 59 per cent., with a gain of 1,500,000 red cells in one month. Each of these patients received two transfusions. In 6 there were gains of only a few points, and in 4 there was no definite improvement. In 1 the hemoglobin percentage and erythrocyte count fell, but later, after splenectomy, improvement occurred.

In general, preoperative transfusions have proved valuable in improving the general condition of the patient and in favorably affecting the blood-picture. The hemoglobin percentage and the red cell count have been moderately raised, and the characteristics of the blood count favorably affected. Our knowledge of the hematopoietic system indicates that a consistently low leukocyte count with relative and absolute reduction in polymorphonuclear cells is to be interpreted as the result of severe injury to the bone-marrow. Transfusion is usually followed by a gradual slight rise in the leukocyte count and an increase in the absolute number of polymorphonuclear cells. This reaction is not, however, to be compared in degree with that following splenectomy, which, on the other hand, must be considered in the light of postoperative leukocytosis in general.

Splenectomy.—That definite benefit for a period of months follows splenectomy in a high percentage of the cases seems to be clearly indicated by a study of this series. Of 28 patients recovering from operation, there was a gain during the first period of three months in 22 (78 per cent.). During the second period of three months, 11 (68 per cent.) of 16 patients then living maintained their gain. This gain represents

a satisfactory, and in several instances a remarkable, improvement in the blood-picture and the general condition. It has, however, little relationship to spinal cord symptoms or signs. Two living patients have maintained a satisfactory condition for one year, three for nine months, and three for six months (Tables 1 and 2).

TABLE 1.—SPLENECTOMY FOR PERNICIOUS ANEMIA

	CASES
Total (April 1, 1916)	31
Operative deaths (9.7 per cent.)	3
Recovered from operation	28
Marked and continuous gain after splenectomy during the first three months' period	22
Number of cases recorded during second three months' period	16
Number of patients maintaining gain during second three months' period	11
Relapse	3
Postoperative deaths	5

TABLE 2.—SPLENECTOMY FOR PERNICIOUS ANEMIA: CONDITION OF PATIENTS IN THREE-MONTH PERIODS AFTER OPERATION WITH RESPECT TO BLOOD AND GENERAL CONDITION*

CASE AND NUMBER	DATE OF OPERATION	OPERA-TIVE DEATH	MONTHS				
			3	6	9	12	15
1. 7,040 E. P. F.	2/10/10	..	—	?	..	..	D†
2. 112,160 D. M.	8/11/14	..	+	+	—D	.	
3. 98,744 M. S.	12/ 2/14	..	—D				
4. 122,468 J. B. M.	1/23/15	..	—D				
5. 124,257 M. S.	3/10/15	..	+	+	—R	+	—R
6. 127,677 C. H.	4/17/15	D					
7. 129,678 O. D. B.	6/ 4/15	..	+	+	+	+	
8. 128,367 J. H. D.	6/ 5/15	..	+	+	+	+	
9. 131,876 E. S.	6/24/15	..	+	+	—R	D	
10. 131,901 R. C.	7/ 3/15	D					
11. 136,882 M. J. F.	8/ 2/15	..	+	+	+		
12. 134,484 W. G.	8/31/15	..	+	—R	+		
13. 139,695 F. L.	9/ 8/15	..	+	—R	+		
14. 140,045 G. L.	9/30/15	..	+	+	+		
15. 142,349 E. O.	10/ 1/15	..	+	+	+		
16. 141,771 H. F.	10/12/15	..	+	+			
17. 142,587 H. W. L.	10/15/15	..	—	—			
18. 140,970 W. A. S.	10/19/15	..	+	+			
19. 133,078 C. A.	10/25/15	D					
20. 134,232 J. M.	10/26/15	..	—	—			
21. 147,503 E. F.	12/31/15	..	+	+			
22. 150,807 W. E. B.	2/ 2/16	..	+				
23. 151,068 M. R.	2/14/16	..	+				
24. 150,229 E. S.	2/23/16	..	+				
25. 151,665 F. W. N.	2/24/16	..	+				
26. 152,922 W. H.	3/10/16	..	+				
27. 152,671 H. L.	3/15/16	..	+				
28. 136,512 C. G. T.	3/17/16	..	+				
29. 154,493 D. D. H.	3/25/16	..	+				
30. 153,395 L. C. H.	3/29/16	..	+				
31. 151,646 B. N.	3/29/16	..	+				

* In this table + indicates gain, — loss, R relapse, and D death.
† Death at end of three years.

In the course of pernicious anemia, splenectomy seems to cause a more profound immediate reaction than any other form of treatment. This is demonstrated by our observations chiefly in three ways: (1) By an improvement in the blood-picture and a change in its characteristics: (2) by a gain in the general condition, and (3) by a fall in the values of the blood-derived pigments in the duodenal contents.

1. *The Blood-picture.*—The very prompt occurrence of leukocytosis with a corresponding increase in the relative and absolute polymorphonuclear neutrophil count, together with showers of normoblasts, is indicative of a very marked reaction after splenectomy. The average leukocyte count in these cases within a few days of operation was 11,531. A very high polymorphonuclear count was almost constant. This leukocytosis persisted at least for a period of months. One month after operation it averaged 11,473. In cases of which we have record, from three to six months following splenectomy it averaged 10,283. The leukocytosis following splenectomy for pernicious anemia differs from the leukocytosis following operations in general both in degree and in persistence. The polymorphonuclear cells, it is agreed, have their origin in the bone-marrow, and their increase may be the result either of bone-marrow stimulation or of decreased blood destruction. No similar reaction is seen following transfusion.

Large numbers of normoblasts were found in the blood-smears in 25 cases. The average was 56 in a count of 300 leukocytes. This is exclusive of one case in which 536 were recorded.

The gain in hemoglobin is gradual in most cases. The average gain in 20 patients whose condition is satisfactory was from 38 per cent. just preceding splenectomy, to 72 per cent. at periods varying from one month to six months following operation. In three patients it reached 90 per cent. or more.

The increase in the erythrocyte count ran parallel to the rise in hemoglobin. The average erythrocyte count in the 22 cases showing a gain was 2,000,000 just preceding splenectomy, and 3,490,000 at periods varying from one month to six months after operation. In one patient it reached 5,200,000 cells; in seven it rose to over 4,000,000. This improvement was independent of preoperative transfusion, as is evidenced by the fact that nine patients in whom preoperative transfusion was not given showed an average gain from 1,900,000 to 3,700,000. On the other hand, the greatest average gain was seen in 13 patients as a result of combined preoperative transfusion and splenectomy—an average gain

from 1,200,000 to 3,500,000. Postoperative transfusion has been given only in relapses, and not as a routine procedure following splenectomy.

It seems to be clear, therefore, that the blood-picture is more decidedly and consistently influenced by splenectomy than by any other method of treatment. It has not yet been shown that this improvement is more than temporary. A polymorphonuclear increase which persists for months, great numbers of normoblasts, and a gradual rise in the hemoglobin and the red-cell count are most prominent.

2. *The General Condition.*—An improvement in appetite and in general strength has been noted during the early weeks following splenectomy. This has been recorded even before any decided improvement in the blood has taken place. The patients seemed to be less toxic. All but two promptly lost their icteroid tinge. Elimination or partial elimination of some product of altered metabolism or hemolysis would explain the change in the general condition. The psychic effect of surgical treatment has been minimized by a previous explanation of our incomplete knowledge concerning the results.

3. *The Fall in the Values of the Blood-derived Pigments in the Duodenal Contents.*—The increase of urobilin in stools of patients suffering with hemolytic types of anemia and its marked decrease after splenectomy have been demonstrated by Eppinger[2] and his co-workers. The clinical importance of the estimation of urobilin in the excretions in various types of anemia is shown by the work of Wilbur and Addis.[3] The quantitative estimation of urobilin and urobilinogen spectroscopically in Wilbur and Addis units has been successfully applied to the duodenal contents by Schneider.[4] We have estimated the values of the blood-derived pigments in the duodenal contents of 34 patients, and our findings in general corroborate those of Schneider. The only results I report at this time were obtained in 9 cases of this series. The very striking fall in the values of the blood-derived pigments after splenectomy would seem to indicate a favorable effect with respect to the hemolytic factor. The values frequently run parallel to the degree of icterus (Table 3). In one case the total estimation of urobilin and urobilinogen fell from 6000 units before operation to 800 twenty-one days afterward; in another, from 5000 units to 200 units. That this marked reduction in bilirubin, urobilin, and urobilinogen in the duodenal contents will prove constant or that it will obtain at a later period, after splenectomy, we have yet no indication.

'16—46

TABLE 3.—ESTIMATION OF HEMOGLOBIN-DERIVED PIGMENTS IN
DUODENAL CONTENTS, WILBUR AND ADDIS UNITS
(SCHNEIDER TEST)

Case and Number	Time Before and After Splenectomy	Color	Bili-rubin	Uro-bilin	Urobilin-ogen	Total
5. 124,257 M. S......	12 months after	......	+	400	0	400
22. 150,807 W. E. B....	37 days after	Yellow	++	700	0	700
24. 150,229 E. S........	30 days after	Yellow	+	1,700	0	1,700
25. 151,665 F. W. N....	34 days after	Yellow	....	600	0	600
26. 152,922 W. H......	7 days before	......	+++	2,000	600	2,600
	21 days after	Yellow	+	1,400	0	1,400
27. 152,671 H. L.......	20 days before	Dark brown	....	6,000	4,000	10,000
	14 days before.	Dark brown	....	5,000	1,000	6,000
	21 days after	......	....	800	0	800
28. 136,512 C. G. T.....	15 days before	Dark brown	+++	2,200	600	2,800
29. 154,493 D. D. H....	9 days before	Dark brown	+	3,000	2,000	5,000
	17 days after	Yellow	....	200	0	200
30. 153,395 L. C. H....	9 days before	Dark brown	+++	3,500	Trace	3,500
	24 days after	Yellow	Trace	200	?	200

Can we formulate what might be termed a balance between the hemolytic and myelotoxic factors in a given case? Between blood destruction and blood production? The values for the blood-derived pigments, it would seem, should in some measure be an index of hemolysis; on the other hand, the characteristics of the blood-picture, if we can properly interpret them, are doubtless expressive of the condition of the bone-marrow. Decided fluctuations in the leukocyte count and in the characteristics of the differential count are seen in many cases of this series, both before and after transfusion and before and after splenectomy. There is considerable evidence to indicate, however, that a consistently low leukocyte count with a reduction of the polymorphonuclear neutrophils is indicative of severe bone-marrow insufficiency. Certainly a constant complete inversion of polymorphonuclear and lymphocyte percentages, that is, a very low polymorphonuclear percentage with a high lymphocyte percentage, is an unfavorable indication, though it does not mean that a subsequent remission may not occur. If in spite of active hemolysis a patient with high hemolytic values is able to maintain a blood-picture with favorable characteristics and only moderate anemia, there should be present an active bone-marrow, and the case would appear to be a more favorable one for splenectomy. Irrespective

of high or low hemolytic values, if the leukocyte count is consistently low, with an inversion of the differential count, and the anemia extreme and showing no reaction after transfusion or medicinal treatment, the case would seem to be an unfavorable one because of probable advanced pathologic changes in the bone-marrow.

Age.—The largest number of patients (twelve) were between forty and fifty years of age.   One was in the second decade, three in the third, five in the fourth, eight in the sixth, and two in the seventh.

The progress of the patient in its relationship to age cannot at present be ascertained from a study of these cases.   In general, the older patients presented less evidence of active hemolysis and more evidence of marrow damage.   The patients of middle age were of both the hemolytic and myelotoxic types, while in younger patients hemolysis was usually active.   The severity of the disease varied with the individual case irrespective of age, save that the oldest patients were prone to a chronic form with less definite remissions.   While the younger patients probably are capable of more benefit as a result of bone-marrow stimulation and an amelioration of the hemolytic factor, many patients of the fourth and fifth decades have shown remarkable gains.

Weight of Spleen.—The average weight of the spleens removed in this series was 422 gm., exclusive of two very large spleens weighing, respectively, 1120 and 1600 gm.   In only two cases did the spleen weigh less than 175 gm.   The very small spleen is usually present in the late stages of pernicious anemia, and a moderately enlarged spleen is generally found when hemolytic activity is marked.   Splenectomy influences chiefly the hemolytic factor of the disease, and one might argue that the presence of a moderately enlarged spleen is a point of evidence in favor of splenectomy.

Operative Mortality.—In this group of 31 cases there were 3 operative deaths, giving an operative mortality of 9.7 per cent.*   There is no apparent reason why the operative mortality of splenectomy for pernicious anemia should not be low when a proper operative selection has been made.   The spleen is relatively small, adhesions usually insignificant, and the technical procedures not difficult.   The risk of surgical treatment is decidedly increased in patients with severe anemia, and every

* Forty-seven splenectomies for pernicious anemia have been done to September 1, 1916, with three operative deaths, an operative mortality of 6.4 per cent. There have been no deaths in the last 29 cases.

endeavor should be made to improve the hemoglobin to 35 or 40 per cent.. and the erythrocyte count to 1,500,000 cells.

A consideration of the features presented by the three patients who died following operation reveals that one of them was distinctly not a case for surgical treatment. The hemoglobin was 19 per cent., even after two transfusions, and a consistently low leukocyte count was present. The other two operative deaths were similar in character, and presented unusually striking features. The patients died, respectively, on the third and fourth days after having suddenly developed fever as high as 106° F. and delirium, in one case associated with hyperpnea and pulmonary edema, and in the other with persistent vomiting and ultimate coma. Postmortem examination in both instances failed to show a sufficient cause for death. These fatal attacks may have been the result of operation at a time of recrudescence or impending crisis; in one instance acidosis is a probability. Neither of these patients was in a weakened condition before operation, but both of them for two weeks previous to operation showed a falling hemoglobin, a decrease in the red blood-cell count, and a low and falling leukocyte count, all of which would at present be regarded as points in evidence against a recommendation for surgery.

Postoperative Death.—Five patients who recovered from operation died subsequently. In two the downward course was not averted by splenectomy, and death occurred at home within three months. In one of these patients there was a slight gain in the condition of the blood. but a double femoral thrombophlebitis developed, and she died with septic manifestations. In the second patient there was no reaction either in the general condition or in the blood, and a steady decline occurred. The spleen in this instance was very much above the average size for pernicious anemia, weighing 1120 gm. A third patient died at nine months after decided improvement which was maintained for approximately six months. A fourth patient died at twelve months after gaining to 90 per cent. hemoglobin and 4,000,000 red cells and maintaining a good condition for seven months. The fifth patient died three years after splenectomy; his postoperative course was never determined.

Relapses.—Three living patients have had relapses, two within six months following operation after an improvement during the first period of three months, and one at fourteen months after recovery from a previous relapse at nine months. Two of these who were treated by

transfusions at the time of relapse have again had remissions. Three additional patients have never shown evidence of definite gain since splenectomy.

SUMMARY

1. There is no evidence that splenectomy has cured pernicious anemia.

2. A review of 31 cases of splenectomy for pernicious anemia demonstrates a definite gain in the blood, the weight, and the general condition during the first three months of the postoperative period in 78 per cent. of the cases; during the second three months' period, 68 per cent. of living patients maintained their gain.

3. A consideration of the advisability of splenectomy would seem to be warranted at present chiefly in young and middle-aged patients of good general resistance, who show evidence of active hemolysis and in whom the spleen is moderately enlarged.

4. The estimation of the blood-derived pigments in the duodenal contents is valuable in determining the degree of hemolytic activity present at a given time. A comparison of the degree of hemolysis with the severity of the anemia would seem to be indicative of the productive power of the bone-marrow.

5. Preoperative treatment, especially transfusions, should be employed to influence the general condition of the patient and to improve the characteristics of the blood-picture. The operative risk is increased when the hemoglobin is below 35 per cent. and the erythrocyte count less than 1,500,000 cells.

6. Postoperative transfusions have not been given as a routine procedure, but transfusions have been successfully employed in postoperative relapse.

REFERENCES

1. Moffitt, H. C.: "Studies in Pernicious Anemia," Amer. Jour. Med. Sci., 1914, cxlviii, 817–827.
2. Eppinger, H.: "Zur Pathologie der Milzfunktion," Berl. klin. Wchnschr., 1913, l, 1509–1512, 1572–1576, 2409–2411. Eppinger, H., and Ranzi, E.: "Ueber Splenektomie bei Bluterkrankungen," Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1914, xxvii, 796–806.
3. Wilbur, R. L., and Addis, T.: "Urobilin: Its Clinical Significance," Arch. Int. Med., 1914, xiii, 235–236.
4. Schneider, J. P.: "Splenic Pathology of Pernicious Anemia and Allied Conditions: A Duodenal Method of Estimating Hemolysis," Arch. Int. Med., 1916, xvii, 32.

In addition to the references already given, the following will be found of interest:

Archibald, A.: "Transfusion in the Treatment of Pernicious Anemia," St. Paul Med. Jour., 1917, xix, 43–47.

Balfour, D. C.: "Indications for Splenectomy in Certain Chronic Blood Disorders: The Technic of the Operation," Jour. Amer. Med. Assoc., 1916, lxvii, 790–793. "The Spleen in Its Relationship to Pernicious Anemia, Splenic Anemia, and Hemolytic Jaundice," Canad. Med. and Surg. Jour., 1916, xl, 47–57.

Krumbhaar, E. B.: "Late Results of Splenectomy in Pernicious Anemia: A Statistical and Critical Review," Jour. Amer. Med. Assoc., 1916, lxvii, 723–727.

Lee, R. I., Minot, G. R., and Vincent, B.: "Splenectomy in Pernicious Anemia: Studies on Bone Marrow Stimulation," Jour. Amer. Med. Assoc., 1916, lxvii, 719–723.

McClure, R. D.: "Pernicious Anemia Treated by Splenectomy and Systematic, Often-Repeated Transfusion of Blood: Transfusion in Benzol Poisoning," Jour. Amer. Med. Assoc., 1916, lxvii, 793–798.

HEAD, TRUNK, AND EXTREMITIES

EARLY OPERATION FOR SEVERE INJURIES OF THE HEAD.—REPORT OF TWO CASES OF MENINGEAL HEMORRHAGE*

EMIL H. BECKMAN

One is impressed with the number of people seeking relief from a great variety of symptoms which are the result of previous injuries of the head. The most common of these symptoms are headache, vertigo, throbbing sensation in the head, defective memory, various degrees of aphasia, and convulsions.

The usual history is one of injury to the head accompanied by loss of consciousness continuing from a few minutes to several hours. Often there is bleeding from one ear or the nose. After a few hours the conjunctivæ become ecchymotic. There are one or more convulsions. Varying degrees of aphasia may be present. Later the mind becomes clearer, and the patient is able to be up and about. The attending physician and the family then give a long sigh of relief and hope that all danger has passed.

The patient gets around slowly, takes little interest in affairs, is slow of speech, complains of headache, vertigo, drowsiness, and just when every one is feeling he has almost, if not entirely, recovered he has another convulsion. His physician is hastily summoned, a second and often a third are called in consultation, and after a brief conference it is decided best not to wait longer, but to "resort to surgery."

In the treatment of injuries of the head several points should be especially emphasized. The brain is the most delicate of all the structures of the body and can tolerate only a small amount of traumatism. It is inclosed entirely by the skull, which is a protection, but this also produces an added risk from increased pressure. If the brain is impinged on by a tumor or blood-clot, it cannot relieve itself of this pressure by a change in its position, as so often occurs with other organs.

It is estimated that an increase of one-fifth in the normal capacity of the cranium will produce disastrous results. It is also estimated that total anemia of the brain-cells for as long as seven minutes prevents their regeneration.

Careful observers have known for a long time that fractures of the skull in which the dura was ruptured were much more favorable than similar fractures with no laceration of the dura, the reason being that the rent in the dura acts as a means for the escape of blood and cerebro-spinal fluid and affords a means for relief of pressure.

The mortality in brain injuries will always remain high because in many instances the trauma has produced lacerations of the substance of the brain, and injured the circulation or the basal ganglia to such an extent that recovery is impossible. On the other hand, there is a very large proportion of cases in which death, or partial or complete incapacity, is due not to the injury *per se*, but to the intense intracranial pressure which follows. This intense intracranial pressure is most often due to hemorrhage from one of the large vessels, but may occur from edema; but whatever the cause, it is of vital importance that it should be relieved as early as possible.

In this type of cases early operation for the relief of tension is imperative: (1) To prevent a fatal issue, and (2) to prevent the distressing complications that so often follow, chief of which are paralysis and epilepsy.

Statistics show that 90 per cent. of meningeal apoplexies are fatal without operation, while in a large series of patients operated on 67 per cent. recover—a percentage which would be much larger were it possible to secure prompt intervention before the usual onset of medullary symptoms in those patients in whom the extravasation takes place rapidly.

The above statistics offer the best argument that can be advanced in favor of early operation. Medical students and the profession generally should be impressed with the fact that early relief of tension by surgical means offers the only hope of relief in many instances. Late operations for traumatic epilepsy and paralysis are most disappointing, and but rarely does the patient receive the expected relief. A late operation for a head injury is like obtaining life insurance after the age of fifty. One loses the protection so sadly needed earlier, and the premiums one must pay are so high as to be almost if not entirely prohibitive. The following cases illustrate the value of early operation:

CASE 1 (A136,278).—A young unmarried man, aged twenty-eight, was hit with a baseball, about 3 o'clock one afternoon, in the left temporal region. He became unconscious immediately, but recovered consciousness in a few minutes. He was then able to walk some distance to his home. During the night he had several convulsions, each one of which lasted two or three minutes. He became more and more stupid and had increasing difficulty with his speech. He came under our observation the following morning, eighteen hours after the injury. Examination revealed swelling over the left temporal region, with a blood-clot in the soft tissues. The skin was not broken; there had been no bleeding from the nose or ears. The conjunctiva was not injected. The patient was drowsy, but could be easily aroused. He had great difficulty in speaking and could pronounce but a few words.

Operation: Craniotomy.—A good-sized osteoplastic flap was turned down from the left motor area. A blood-clot two inches in extent and one-half inch thick was at once seen lying over the lower end of the fissure of Rolando. When this clot was removed, bleeding occurred from the middle meningeal artery at a point corresponding to the center of the clot. The vessel was ligated. The dura was opened. There was no hemorrhage inside the dura. No laceration of the cortex or fracture of the skull could be determined. No convulsions followed the operation. His stupor improved, and he gradually regained complete power of speech. Full control of speech did not return for about six weeks. He was examined three months after the injury, at which time he was in perfect health, no dizziness or headache, speech was normal, and he had resumed his occupation as a farm laborer.

CASE 2 (A134,940).—Unmarried man, aged twenty-five. This patient was hit in the left temporal region by a baseball. He immediately became unconscious and had bleeding from the left ear. He regained consciousness in about fifteen minutes and was able to drive his automobile home. After three days he resumed work as a farmer, and felt perfectly well, with no headache or focal symptoms. Ten days later he developed a headache and a convulsion with unconsciousness which lasted half an hour. Upon regaining consciousness there was some interference with the power of speech. The following day he had so far recovered that he was able to drive his father in an automobile some distance. Later in the day he had to go to bed again, had another severe convulsion, with unconsciousness which lasted an hour. From that time until he came under observation, three weeks after the injury, he had many light convulsions—ten in twenty-four hours.

At that time he was somewhat slow in replying to questions, but the power of speech was almost normal. He was able to be up and about except during his convulsions. There were no wounds of any kind on the head; the skin had never been broken.

Operation: Craniotomy.—A good-sized osteoplastic flap was turned

down from the left temporal and motor area. No fracture of the bone could be found. The dura was not lacerated, and there were no blood-clots outside the dura. Upon opening the dura yellow serum escaped and a large, partially organized blood-clot, four inches in extent and nearly one-half inch thick at the thickest portion, was seen covering the motor area and extending well down onto the temporal lobe. The clot was organized enough so that it was easily separated from the dura and from the cortex. When it was removed, it was nearly four inches across and resembled a good-sized pancake. There was no fresh bleeding, and the source of the hemorrhage could not be made out, but since the thicker portion of the clot was directly beneath the middle meningeal artery, we believed that this vessel furnished the hemorrhage. The patient had a slight convulsion the evening after the operation. He was under observation for two and one-half weeks. The drowsiness disappeared and there were no further convulsions.

If these patients had been allowed to continue without operation, it is very probable that at least one of them would have become an epi-leptic. It is also more than likely that the other would have suffered from aphasia of a greater or less degree.

OBSERVATIONS ON THE DIAGNOSIS AND TREAT-
MENT OF TRIFACIAL NEURALGIA *

EMIL H. BECKMAN

— — -

These conclusions are based on the results of treatment in 177 cases
of trifacial neuralgia which have come under our observation.

Diagnosis.—Trifacial neuralgia is not often confused with any other
disease by those who have seen a number of cases. It is a disease that
has a distinct entity. In our series, males and females were about
equally affected (male 96, female 81). A great many cases in which
there was pain about the head and face due to sinus disease, disease of
the nose, and infection about the teeth or jaw are confused by the aver-
age practitioner with facial neuralgia and referred to the surgeons or
neurologists as such. All cases of this nature have been excluded from
this series.

The term tic douloureux is a misnomer, since there is no true spasm
of the muscle associated with the pain. This muscular spasm occurs in
only a small percentage of the cases, and is a voluntary or involuntary
jerking of the muscles resulting from the sudden severe pain; the pa-
tient is startled by the lightning-like pain, and the muscles of the face
are contracted in consequence. Many patients attempt in every way
possible to immobilize the muscles of the face for fear the attack may
continue. Consequently, they refuse to speak in answer to questions,
refrain from taking food or drink except when necessity demands it,
and delay bathing the face as long as possible. The pain is always
severe, and comes in a short, sharp attack, like a shock of electricity.
If the attack continues for a half-minute or longer, it will be found on
close questioning that the pain is not continuous, but is made up of a
series of short, severe attacks interrupted by brief intervals. We have
not seen cases in which the pain was of any other character.

A continuous aching pain or pain that throbs with the pulse certainly

is not trifacial neuralgia. From our observations, and as Patrick has so graphically pointed out, the pain is very often started by the slightest irritation of a certain localized area on the face or tongue, and occasionally by the irritation of a single tooth. These areas have been described by Patrick as "doloro genetic zones" or "trigger zones," which is a good description, since the slightest irritation of one of them is comparable to the lightest touch on the hair-trigger of a gun, and explosive pain follows the irritation immediately. The cause of the irritation may be very slight—a draft of air, a touch with cotton, or the lightest touch of a finger. In individual cases the pain is invariably started by irritation of the same area.

The zones from which the pain most often originates are small areas on the upper lip, just at the alæ of the nose, and on the lower lip near the vermilion border at the angle of the mouth. These two points seem to predominate over all others. The pain produced by stimulating one of these trigger zones may not be confined to the same division of the nerve as the trigger zone itself. For instance, touching the upper lip at the angle of the nose may produce pain in the lower lip, lower jaw, or tongue. Vice versa, stimulation of the lower lip or third division may produce pain in the second. Rarely does the stimulation of one division produce pain in another that is not adjacent. This has been such a common observation with us that when treating with injections we have adopted the plan of always injecting both the second and third divisions when but one of them is affected.

Our patients have not appeared to be more neurotic than the average. Most of them had never had any serious illness and were in good health so far as could be determined from their appearance and their examinations. Infection about the teeth and face is a very usual history, but since these are common to all persons, it is questionable whether they have any real bearing on this disease. It is quite possible that later investigations will show that trifacial neuralgia is an infection of the nerve-branches which progress to the Gasserian ganglion. At least a great many patients who have had pain in a single peripheral nerve and who have been relieved by the removal of this peripheral branch have later returned with pain in another division or in all three divisions. This makes it appear that the disease might be progressive, extending from the periphery toward the ganglion. We have no proof to corroborate this theory except that it is known that certain bacteria have a selective affinity for nerve tissue as their habitat. Examination of

six ganglia. from trifacial neuralgia cases by Wilson showed marked inflammation in all. The average age was 50.6 years. We have not felt that arteriosclerosis plays any rôle in this disease. Heredity, rheumatic tendencies, or extreme nervousness has not seemed to have any influence. The fact that people who suffer agonies for years almost never become addicted to the use of morphin or cocain (one patient in this series addicted to both) seems to indicate that at least their mental, if not their nervous, stability is above the average.

Treatment.—The treatment of trifacial neuralgia is essentially surgical. Medical treatment is confined to hygienic measures and seems to have but slight influence in the majority of cases.

Excision or Evulsion of the Peripheral Nerve Branches.—An excision or evulsion of the peripheral nerve branches was done in 19 cases. Three were supra-orbital, 9 infra-orbital, 5 inferior dental, and 1 lingual. Letters have been received from 10 of these patients. The longest period of relief in any of the series was two years. This was a patient in whom the infra-orbital nerve was evulsed and a screw placed in the foramen. Only 5 of the patients were relieved for one year or longer. The average time of relief was 8.4 months. Some of these patients had deep injections of alcohol subsequently and, therefore, have been included among those listed later, in the discussion of that method of treatment. None of the patients treated by excision or evulsion of the peripheral branches had any complications following treatment, and there has been no mortality in this group. The method of Kanavel for blocking the foramina seems to be the most rational that has been proposed, and although we have had no experience with it, we believe it should give better results than the older methods.

Injecting Alcohol into the Main Nerve Branches at the Base of the Skull. —Several years ago we adopted the method of Levy and Baudouin for injecting the deep branches of the nerve. We have treated in this way a total of 146 patients. Letters have been returned from 120. We have followed the method of inserting the needle the average distance for each branch and then moving it a little deeper, slowly, so that when the nerve was approached the patient would receive a shock of pain over the distribution of the branch. From this it is often possible to know that the nerve has been entered, or at least approximated very closely. This is especially true if there have been no previous injections. After the shock of pain has been noted we have injected from 15 to 30 minims of 80 per cent. alcohol. We have not become skilful enough to locate

the nerve each time an injection is made. In fact, this seems to be impossible. If the nerve is entered or approximated very closely, the patient will be relieved, at least temporarily. As mentioned previously, the plan has been followed of injecting both the second and third divisions when one of them was affected. Occasionally some bleeding resulted, which produced considerable tension underneath the temporal fascia. In three patients there was inflammatory reaction of the cornea which cleared up within a few days; in two there was temporary paralysis of the external rectus muscle of the eye, and in six, stiffness of the muscles of mastication, which gradually subsided. The latter were patients who had had several injections. The length of time patients were relieved varied greatly, in one instance the relief lasting as long as five and one-half years, in another three years, and still another three and one-half years. This would seem to be very favorable. However, only 30 were relieved for one year or longer. The average length of time for the entire series of 120 from whom we have heard was 9.4 months, a slightly longer average than the time of relief following our series of operations on the peripheral branches. A discouraging feature of this method of treatment is that 77 of the 120 (64 per cent.) had relief of pain for six months or less. There has been no mortality in this series and no serious complications. More recently the injection of alcohol into the Gasserian ganglion itself has been proposed. The technic of this operation has been perfected largely by Fritz Härtel, of Bier's Clinic, and by Urban Maes in this country. Maes reports that Härtel has injected 27 patients by this method and is satisfied with his results, reinjection rarely having been necessary. Maes himself treated his first case by this method in June, 1913, and reports lasting relief. He does not mention any other results. Up to the present time we have no evidence to show that the results following injection of the ganglion itself will be more permanent than injection of the deep branches. I can testify that isolation of sensory nerves elsewhere in the body with injection of a considerable amount of alcohol into their main trunks does not always give freedom from pain. We have no personal experience with injections into the Gasserian ganglion. If this method of treatment becomes generally adopted, I feel certain that there will be many serious complications.

Operation on the Gasserian Ganglion.—Eighteen patients have had operations on the Gasserian ganglion. Twelve of these were males and

6 females.   The average age was forty-eight years;   the youngest was thirty years of age and the oldest seventy.   Thirteen of these patients had had some type of peripheral operation, and 2, previous operations on the Gasserian ganglion, while all of them had had deep injections of osmic acid or alcohol into the various nerve branches for the relief of their suffering.   In 9 of these patients all three divisions were involved; in 6 there was involvement of the second and third divisions;   in 2, involvement of the first and second; and in 1, involvement of the first and third.   Eleven patients had the ganglion removed after the Hartley-Krause method, 1 was operated on by the method of Abbe, and 6 by the method of Frazier.   Thirteen of the 16 living patients have been completely relieved of their pain, or the recurrences have been so slight that they consider their condition satisfactory.

The remaining 3 patients of this group have had recurrence.   Two of these were operated on by the Hartley-Krause method and 1 by evulsion of the posterior nerve root.   These recurrences must be considered, we believe, as due to the failure to remove either the entire ganglion or all the fibers of the posterior root, a possibility in early cases when the operator's experience has not been extensive.   My own experience would seem to show that enough emphasis has not been laid upon the one point of getting well behind the ganglion in order to expose all the posterior root, especially to the inner side, before sectioning or evulsing it.   I believe the failure in one instance was due to this fact.

There were two operative deaths in this series.   One of them was that of a woman, sixty-one years of age, who previously had had an operation for the deep removal of the second and third divisions and later an attempt to remove the Gasserian ganglion, both of these before she came under our observation.   She died from late hemorrhage on the twenty-first day after operation.   Undoubtedly the enormous amount of scar tissue from the two former operations was largely responsible for the fatal termination.   The other patient, a woman forty years of age, never rallied from the operation, and died about twelve hours after leaving the operating room.   Unfortunately, a necropsy in this case could not be obtained.   I am satisfied that hemorrhage was not the cause of death in this instance.

The results of operations on the Gasserian ganglion, according to this series, are not entirely satisfactory, but probably this is due largely to the fact that some of the patients were operated on several years ago when experience in this work was not great.   In our opinion the same

'16—47

number of patients operated on to-day would give approximately 100 per cent. permanent relief from pain.

The mortality in this series is much too high, and that of many a larger series of cases may be lower. However, the operation is serious and must not be undertaken too lightly. Surgeons who have not had considerable experience in surgery of the brain should not undertake the operation. The mortality as well as the permanent results may be improved only by those who have had such experience and are willing to do the most painstaking and careful work. In my own work the more Gasserian ganglia I dissect on the cadaver the more I feel that it is a difficult and serious operation and that only when it is performed with the utmost care can one feel sure that all the nerve-fibers have been removed in an individual case. At the present time evulsing the posterior nerve root or removing the ganglion entirely is the only operation insuring permanent relief, and the mortality is no higher than that of many serious operations performed daily by surgeons throughout the country. Therefore, since patients with trifacial neuralgia do not recover spontaneously and the results of peripheral operations and injections are so temporary, this should be the operation of choice for a person in reasonably good physical condition.

REFERENCES

Patrick, H. T.: "The Treatment of Trifacial Neuralgia by Means of Deep Injections of Alcohol," Jour. Amer. Med. Assoc., 1907, xlix, 1567–1573. "The Technic and Results of Deep Injections of Alcohol for Trifacial Neuralgia," ibid., 1912, lviii, 155–163.

Lévy, F., and Baudouin, A.: "Les injections profondes dans le traitement de la névralgie faciale rebelle," Presse méd., 1906, xiv, 108.

Härtel, F.: "Ueber die intracranielle Injektionsbehandlung der Trigeminusneuralgie." Med. Klin., 1914, x, 582–584. "Die Behandlung der Trigeminusneuralgie mit intrakraniellen Alkoholeinspritzungen," Deutsch. Ztschr. f. Chir., 1914, cxxvi. 429–552. Gives excellent bibliography.

Maes, U.: "The Treatment of Trifacial Neuralgia by the Intraganglionic Injection of Alcohol (Härtel's Method)," New Orleans Med. and Surg. Jour., 1913–1914. lxvi, 183–188. "The Surgical Treatment of Tic Douloureux," International Abst. Surg.. 1915, xxi, 349–359. Gives excellent bibliography.

ROENTGEN DIAGNOSIS OF BRONCHIECTASIS *

ALEXANDER B. MOORE

— — —

That the roentgen rays furnish more or less definite information in the diagnosis of bronchiectasis has long been recognized; but a review of the literature impresses one with the chaotic state of mind of most observers in regard to the cardinal points on which the roentgen diagnosis is based, and the difference in opinion existing among internists as to its relative value. Most observers agree that the ordinary methods of chest examination—percussion and auscultation—are of questionable value in bronchiectasis, the diagnosis usually being based on the history of cough, profuse expectoration, and a proper exercise of the olfactory sense. That a diagnosis based on such data is often erroneous may be easily understood when it is considered that these features are equally essential in the diagnosis of abscess of the lung and chronic bronchitis.

The object of this paper is to emphasize certain facts long known to roentgenologists and to impress on the internist the fact that the roentgen rays furnish us with most valuable information in the diagnosis and differential diagnosis of bronchiectasis.

The relative failure of medical treatment in these cases and the success that has attended surgery, when proper care is exercised in selecting cases for operation, renders it essential that all available diagnostic means be employed to determine the nature and extent of the process. The roentgen rays offer in a large percentage of these cases the only means of ascertaining the true nature, extent, and location of the affection, such information being absolutely essential in the selection of the course of treatment to be pursued. As has been emphasized by Jackson, the possibility of the presence of a foreign body, even without history, must be considered in all cases of bronchiectasis, thereby adding another reason for routine roentgen examination. The number of

these cases that have been diagnosed in the past as tuberculosis, or in which the patients have been subjected to a thoracotomy and drainage operation under the mistaken idea that the condition was either an abscess or an empyema communicating with the bronchi, is sufficient proof of the hazy clinical picture that many of these cases present.

Etiology.—While much has been written concerning the etiology of bronchiectasis, it is probably sufficient to say that any condition which tends to weaken the bronchial walls, lessens their elasticity, or increases the pressure within the bronchial tubes, predisposes to this disease. The bronchi and bronchioles are weakened and their resistance is lowered by any bronchial inflammation, either acute or chronic. The inflammatory changes in acute bronchitis and the atrophic changes in the elastic and muscle-fibers in the chronic form may lower the resistance of the bronchial tubes sufficiently to render them unable to stand the strain of any increased pressure. These degenerative changes are most common in bronchopneumonia and bronchitis resulting from whooping-cough, measles, influenza, and fevers. The etiologic importance of bronchopneumonia in particular cannot be too strongly emphasized. Increased pressure in the tubes is usually produced by cough. Cough is probably the most important factor in bronchiectasis, although retention of secretion, such as occurs, for example, when the bronchus is plugged by a foreign body, must also be regarded as of considerable importance. It is highly probable that both foreign bodies and enlarged bronchial lymph-glands produce bronchiectasis more by reason of the associated cough than by the local obstruction they produce. Another factor to be considered is traction on the bronchi and bronchioles due to indurative or cirrhotic changes in the lung, such as occur in tuberculosis, syphilis, and other infections. The fibrous tissue produced by these changes may contract, causing sufficient traction on the bronchi and bronchioles to produce a subsequent dilatation. However, in view of our present knowledge of this disease, it seems probable that bronchiectasis results more frequently from a combination of these causes than from any one alone. Poor hygienic surroundings apparently exert a marked influence in its production, few cases being found in patients living under conditions of proper hygiene. Although the work of Smith and others has established beyond question the importance of the Bacillus influenzæ in bronchiectasis, in the majority of our cases the infection has been mixed.

Types.—Bronchiectasis may be classified from the standpoint of the

roentgenologist as occurring in three types: the infiltrative, the cylindric, and the sacculated. These three forms most probably represent different stages in the disease and demonstrate the existence of gross changes that have been proved by pathologists.

The first or infiltrative type appears in the roentgenogram as a more or less stringy increase in density along the course of the bronchi, usually localized in the lower pulmonary lobes and radiating outward from the hilus to the periphery of the chest and extending into the costophrenic angle. This infiltration in the earlier stages of the disease is not particularly marked and differs little from that seen in chronic bronchitis or other irritative conditions of the bronchial tract, save that the process is usually more localized, is found nearly always at the base of the lung, the bands of increased density extending to the periphery of the chest. It is probable that this stage corresponds to the clinical stage in which drainage is effective and there is relatively little retention of secretion. The infiltrative form of bronchiectasis presents the chief difficulties to the roentgenologist, and in many cases it is impossible to make an unqualified diagnosis.

The infiltrative stage is followed by the cylindric type. There is the characteristic mottled increase in density, extending outward along the course of the bronchi, producing a more or less fan-shaped shadow. The density is usually greatest near the hilus and, distributed throughout this density, one or more small areas of diminished density may be located. These areas are more or less clearly circumscribed and are produced by the so-called pseudo-cavitations of bronchiectasis which are dilated bronchioles that have been emptied of their secretions. The visualization of these cavitations depends largely on the ability of the patient to empty the bronchi of secretion, and their presence is pathognomonic of the disease. Consequently, a doubtful diagnosis is often made certain by a second roentgen examination after the patient has brought up as much of the bronchial secretions as possible. This is most easily accomplished by instructing the patient to cough while in the Trendelenberg position, face down. It is the fan-shaped increase in density along the course of the bronchi and the localization of one or more of these pseudo-cavitations that make the roentgen diagnosis of the cylindric type of bronchiectasis practically certain. However, should the process be confined to that portion of the left lung which is hidden by the superimposed heart shadow, a diagnosis may be impossible. The possibility of the existence of such a condition should, therefore, always

be borne in mind before an unqualified negative diagnosis is given in a case that is clinically suspicious.

The third or sacculated type of bronchiectasis is characterized

Fig. 327.— (171,810.)   Bilateral infiltrative bronchiectasis involving both lower lobes.

roentgenographically by the localization of distinct pseudo-cavitations surrounded by dense fibrous tissue. These cavitations are practically always multiple and larger than those encountered in the cylindric type. They vary in size from that of a bean to that of a walnut and

have a thin wall. The section of a lung involved by the sacculated type of bronchiectasis very strongly resembles a bunch of grapes cut through the center. The fibrous tissue surrounding these groups of sacculations

Fig 328.—(170,877.) Unilateral cylindric bronchiectasis involving middle and lower right pulmonary lobes.

is very dense and often feels like cartilage. It may be so dense and the cavitations may be so filled with secretion that the shadow in the roentgenogram is almost homogeneous and the diagnosis difficult. However, the true condition is usually revealed by emptying the cavities.

Thickening of the pleura, either parietal or visceral, is rather un-
common in bronchiectasis except in those cases in which a previous
thoracotomy has been performed, and it is only in such cases that any

Fig. 329.—(141,430.) Unilateral cylindric bronchiectasis involving middle and lower lobes of the right lung.

marked distortion or limitation in the movement of the diaphragm is
seen. However, in cases of long standing, particularly those of the
sacculated type, the heart and mediastinal structures are often drawn
to the affected side by the contraction of fibrous tissue.

Differential Diagnosis.—The more common conditions from which bronchiectasis must be differentiated roentgenographically are chronic purulent bronchitis and lung abscess.

Fig. 330.—(57,973.) Vacuolar bronchiectasis of right lung. Note large sac in middle lobe. Healed tuberculosis of upper left lobe.

It may be differentiated from chronic bronchitis by the greater increase in density along the bronchial trunks in bronchiectasis, the tendency to localize at the bases of the lungs, the extension of this increased density to the periphery of the chest even as far as the costophrenic

angle, and the presence of bronchiectatic pseudo-cavitation or saccula-tion. Bronchiectasis is usually differentiated without difficulty from abscess of the lung by its location and the fact that the walls of its cavity are relatively thin and small. The cavities are multiple and there is absence of a fluid level within them.

This report is based on a series of 25 cases that have been studied by combined clinical and roentgenographic methods, the findings of which have been tabulated.

The average age of the patients was twenty-six and one-half years, the oldest being forty-eight and the youngest ten years; 14 were males and 11 females. The average time since the symptoms were first noted was eight years. In all but 7 the onset of the disease was described as a cough following an acute infection, commonly measles, whooping-cough, and influenza. The other diseases noted in order of frequency were scarlet fever, pneumonia, and tonsillitis. It seems almost certain that a very large percentage of these cases have their origin in the broncho-pneumonia which is so frequent a complication of these diseases and which contributes so ideally to the production of bronchiectasis. The chief complaint in all of these cases was cough and expectoration. The cough is described as being at first dry, hacking, and unproductive, gradually increasing in severity, tending to become paroxysmal, and gradually more productive. The sputum is at first like that of bron-chitis, consisting of clear mucus. As the disease progresses, the sputum becomes more profuse and more foul, until it may amount to several quarts a day. In appearance, these patients are poorly nourished, anemic, and toxic, with a more or less constant clubbing of the fingers. Nine of the patients in our series had some elevation of temperature when examined, and all gave a history of attacks of chills, fever, and sweats. While such attacks are usually associated by the patients with "taking cold," it seems most probable that they represent a localized bronchopneumonia with congestion and retention of the secretions. The fact that the degree of intoxication from the large amount of putrid material present is not greater is probably due not only to the relative immunity acquired, but also to the comparatively slight absorption that takes place from the walls of the pseudo-cavitations. Seven of the patients have a history of definite hemoptysis, and 12 of an occasional tinge of blood in the sputum. Two patients had inhaled foreign bodies: a splinter of wood in one case, which was subsequently coughed up, and in the other a fragment of tooth which plugged one of the terminal

bronchi, as was found at autopsy. Five patients gave roentgenologic evidences of a tuberculous infection and 3 had tubercle bacilli in their sputum. A definite roentgen diagnosis of bronchiectasis was made in 19 and a diagnosis of probable bronchiectasis in 2. In 4 the roentgen diagnosis was incorrect. The errors in this series occurred in the diagnosis of cases of the infiltrative type in which the condition was confused with bronchitis.

Roentgenographically these cases were classified as follows: Infiltrative, 8; cylindric, 12; sacculated, 5. In 14 cases the condition was bilateral; in 11 cases where the involvement was unilateral 6 were located on the right and 5 on the left side. In the cases in which the process was confined to one lung it involved more than 1 lobe in all but 4. This clearly illustrates the small percentage of cases that are at present diagnosed at a sufficiently early stage to permit of radical surgical interference and the great value of a roentgen examination in determining the extent of the process and the operability of a case.

REFERENCES

Fraenkel, A., and Körte, W.: "Der gegenwärtige Stand der Lungenchirurgie," Berl. klin. Wchnschr., 1912, i, 289–296.

Frik, H.: "Diagnose der Lungenkrankheiten im Röntgenbild," Berl. klin. Wchnschr., 1914, ii, 1336.

Hartshorn, W. M.: "The Roentgen Ray in the Diagnosis of Pulmonary Conditions in Children," Am. Jour. Dis. Child., 1915, ix, 405–417.

Hasselwander, A., and Bruegel, C.: "Anatomische Beiträge zur Frage der Lungenstruktur im Röntgenbild," Fortschr. a. d. Geb. d. Röntgenstrahlen, 1911, xvii, 9–19.

Ingals, E. F., and Friedberg, S. A.: "Fluoroscopic Bronchoscopy," Jour. Amer. Med. Assoc., 1914, lxii, 610–611.

Jackson, C.: "Bronchiectasis and Bronchiectatic Symptoms Due to Foreign Bodies," Pennsylvania Med. Jour., 1916, xix, 807–813.

King, D. B.: "An Inquiry into the Value of the X-rays in Bronchiectasis," Practitioner, 1904, lxxii, 235–250.

Krause, P.: "Über den Wert der Röntgendiagnostik zur Erkennung von Lungenkrankheiten," Ztschr. f. ärzt. Fortbild., 1908, v, 644–647.

Leach, E.: "Bronchiolectasis in Children; with Reference to the Condition Known as Honeycomb Lung from a Clinical Standpoint," Quart. Jour. Med., 1908–9, ii, 251–260.

Orton, G. H.: "The X-Ray Diagnosis of Pulmonary Disease," Arch. Röntgen Ray, 1913, xvii, 402–403.

Pfeiffer, C.: "Zur Diagnose der Bronchiektasen im Röntgenbilde," Beitr. z. klin. Chir., 1906, l, 279–288.

Smith, R. H.: Quoted by Billings. Forchheimer's Therapeusis of Internal Diseases, New York, Appleton, 1915, vol. 3, p. 244.

Von Hoesslin, H.: "Klinisch-röntgenologische Untersuchungen über Lungenkavernen mit Flüssigkeitsspiegel," Arch. f. klin. Med., 1913, cxii, 580–593.

Walsham, H.: "The X-Rays in Diseases of the Chest," Lancet, 1898, ii, 988–991.

THORACIC DISEASES.—THE STATUS OF SURGI-
CAL THERAPY *

SAMUEL ROBINSON

——

In addressing, single handed, a group of practitioners of internal medicine, I realize that I do so at my own risk. I beg your indulgence, however, for my theme is one which vitally concerns us all.

The treatment of diseases of the lung, pleura, and mediastinum is in a lamentably chaotic state. Much has been written on the pathology, bacteriology, and clinical picture of thoracic diseases. But what are we doing which is curative for the mortals thus afflicted? Are we not grossly incompetent? Is it not probable that more coöperation between the internist and surgeon might result in better treatment of the patient? Is the surgeon operating on lesions which the practitioner might cure? Is the practitioner treating some patients unsuccessfully whom the surgeon might cure? Are we sufficiently familiar each with the other's more recent advances in therapy? Or have we perhaps made no advances?

The thoracic cavity is too treacherous a region to become the scene of pastime surgery. The thorax surrenders all playground titles to the pelvis.

Surgery of the pleura begins only at the point where non-operative treatments have failed. Duodenal ulcer may respond to both surgical and medical treatment. Both will be employed. Not so of lesions of the thorax. No surgeon will be fool enough to enter the chest until his "angel brother" internist fears to tread further without success.

No region in the body demands the combined efforts of physician and surgeon more than the pleural cavity. The internist occasionally needs the surgeon, and the surgeon never ceases to require the conservative help of the physician. Therefore, kindly regard us thoracic surgeons

as your servants rather than as your substitutes, as your consultants rather than your competitors.

If we are to be your servants, we must convince you that we are not presumptuous, bold, or boisterous, but rather cautious, conservative, and conscientious.

You will find us useful and safe in the treatment of postpneumonic abscess. We are not unmindful of the high percentage of spontaneous cures by bronchial drainage alone. We urge, however, the privilege of early consultation that we may aid in determining the point at which spontaneous recovery is doubtful and at which the operative risk begins to increase. In such cases ours is a record of extremely low mortality.

In chronic lung abscesses we are less successful. We drain single abscesses and overlook others. We allow our drainage-tubes to produce lung necrosis and fatal hemorrhage. We would welcome the exclusion of this group of cases from the surgical field. We watch with interest your efforts with vaccines, climatic influences, and hygiene, but we grieve at your limited accomplishments.

We believe that early compression therapy in chronic abscess cases will do great good. If you are unsuccessful in collapsing the infected lung with artificial pneumothorax, we would much prefer to operate to strip adhesions, thus facilitating the collapse which you will maintain later, than to be requested at a late hour to perform a drainage operation in a thoroughly septic patient.

Bronchiectasis would seem to be a chronic, incurable disease. The records are hopelessly void of successes without surgery, and painfully attended with fatalities by operation. We venture to suggest that the practitioner withhold such patients with even more than his accustomed tenacity; not obstinately, however, but intelligently.

In true bronchiectasis, expectorants, inhalations, cough mixtures, climatic changes, and vaccines fail. Artificial pneumothorax has been reported as curative. I entertain grave doubts as to the truth of such reports. Either the reported cases have not been true bronchiectasis or a cure has been claimed merely because of a considerable temporary reduction in the quantity of sputum. In three cases of bronchiectasis confined to one lower lobe I have packed the lower pleural cavity with many yards of gauze. A chronic empyema has been artificially produced, with incarceration and compression of the diseased lobe. The quantity of sputum has been slightly reduced; otherwise the disease has continued unaltered. If such radical compression fails to obliterate the cavita-

tions and to produce cicatrization, how much less will the intermittent maintenance of artificial nitrogen pneumothorax accomplish?

Further, do not invite or permit a surgeon to drain your case of bronchiectasis. He will do no good and possibly much harm.

Assuming the correctness of my contention that expectant treatment, vaccine therapy, artificial pneumothorax, and drainage operations are valueless in bronchiectasis, we ask what can be accomplished with our present knowledge? In eight or nine cases out of ten, absolutely nothing which is curative. In the tenth case, however, with the process confined to one lower lobe in a young adult patient with good resistance, further consideration is to be entertained. Look on the pathologic condition of the diseased lobe as beyond hope of correction except by actual removal. Let no man attempt a lobe excision in a single operation. Your otherwise comparatively content and even efficient patient, if thus treated, will soon be dead. A single lobe of the lung may be removed safely in a three-stage or four-stage operation, which I have described elsewhere. Within a year a small series of cases thus treated will be reported. The results so far are certainly most promising. Meanwhile we remain hopeful and open to conviction that internists will substitute a non-operative cure; the surgery of bronchiectasis is at best treacherous and laborious, and, to say the least, filthy.

Emphysema is another stumbling block and again a chronic pathologic condition. Surgery offers but one operation; namely, the removal of several costal cartilages on one or both sides. It accomplishes increased mobility and expansion of an otherwise rigid thorax. In a considerable proportion of cases it relieves distressing symptoms. It does not cure. Heart and kidney complications and suppurative bronchitis are contraindications. Much reduced expansion is the sine qua non of indications. We have too few results on which to base definite opinions as to the value of this procedure, but inasmuch as it is comparatively safe, we urge you to submit cases that we may both know more as to its real significance.

To spare you the mortification of accusing us surgeons of incompetency in the handling of pleural empyema, I will make a series of confessions. Not infrequently we operate for acute empyema and fail to find pus at the very point at which you have recently located it with a needle. You may justly contend that our methods of exploring the pleural cavity are inadequate. If a finger thrust through an opening made by the removal of a half-inch of rib fails to strike pus, naturally

you cannot be entirely satisfied that it is absent. Having urged the internist to prevent the occurrence of chronic empyema by the early detection of pus following pneumonia, we sometimes so badly handle an acute case that it is soon converted into a chronic case. We fail to place the drainage-tubes at the bottom of the cavity. We either apply suction at the expense of drainage or we drain without providing for the expansion of the lung.

These and numerous other surgical errors it is well you should know. You have much to do with the postoperative conduct of empyemas and are justified in demanding that such surgical fallacies be corrected that your patient may more promptly recover. If an operative case of acute empyema is still draining at the end of eight weeks, do not remove the drainage-tubes and trust to the Almighty; do not inject various pastes and solutions or administer vaccines until you have called back the surgeon. 'Point out to him that the roentgen ray shows lack of lung expansion, introduce a probe, and demonstrate the persistence of a considerable cavity. Remove a small piece of tissue at the mouth of the drainage opening, and have a section made and examined for tubercles. Be satisfied only by this procedure as to the possibility of a tuberculous empyema. (Cultures and guinea-pig inoculations from the purulent discharge will rarely prove the presence or absence of tuberculosis.) With such data at your command, the surgeon may admit that the delay in healing is mechanical. He may advise redrainage and freer drainage at a lower point. He should consider the advisability of opening the chest widely and freeing the lung of its adhesions to prevent such fixation as will otherwise result in a chronic empyema.

If despite all such further efforts an empyemic discharge continues four and five months, another surgical consultation is indicated. Probably then a decortication of the lung or some form of osteoplastic operation is indicated to obliterate the cavity. If such is done early when the ultimate necessity is obvious, healing may be complete in less than a year. It is criminal that these patients should be allowed to drift along with chronic sepsis into amyloid disease.

Vaccines may be employed to lessen the profuseness or foulness of drainage, but if designed as a curative measure, necessary surgical measures will be detrimentally postponed. Bismuth and petrolatum should be used in very small cavities, and only when the need of further surgery is excluded.

Of course, the surgeon is essentially at fault in that he does not follow

the progress of each patient with empyema whom he operates on in the acute stage, but I dwell on this subject of empyema to emphasize that surgery properly and persistently applied is the best, if not the only, means of cure. After the primary operation the patients return to you, essentially, perhaps, because the surgeon neglects to follow their convalescence. Apologetically, therefore, we ask your assistance and urge you to demand further surgical intervention when the obliteration of empyema cavities is obviously not progressing.

In the management of tuberculosis, the practitioner has ceased to look to the surgeon for help. Ten years ago, when the experimental removal of large portions of the lungs of animals was first successfully executed, we wondered if such might be possible and feasible in tuberculosis in man. Thus far, however, such is not the case. The removal of the diseased lung of man is associated with obstacles not present in the excision of the normal lung of a healthy dog. Respiratory and circulatory disturbances occur in the process of intrathoracic operating which we are struggling to interpret and overcome, and in the diseased person these complications are exaggerated. The tuberculous patient is a priori a poor surgical risk and the outlook for successful extirpation of tuberculous lung tissue is particularly discouraging. You read of collapsing the tuberculous lung by an extrathoracic operation, pleuropneumolysis, or the resection of numerous ribs to collapse the chest-wall and, therefore, the lungs. Let us suspend such radical and dangerous experiments until we have learned more of the actual value of collapse therapy by artificial pneumothorax. We surgeons may well await your developments with this harmless method before substituting a method that is dangerous. For the present, at least, in those cases in which adhesions prevent the introduction of gases into the pleural cavity, let nature rather than ill-applied surgery take its course.

We do not regard the drainage of tuberculous cavities as a profitable surgical measure. At present writing the only justifiable mechanical procedure in pulmonary tuberculosis is collapsing the lung by the introduction of nitrogen or fluid into the pleural cavity. This treatment is carried on very properly by internists. Suffice it to say that collapse therapy has almost a specific effect in the arrest of pulmonary hemorrhage. In progressive cases with unilateral or even bilateral involvement, symptomatic relief can be expected in 40 per cent. of the cases in which collapse is conscientiously maintained. The disease is arrested

in a considerable number of cases of the progressive type; 13 per cent. would not be an exaggerated estimate.

I am involved in the study of a group of cases which we have doubtless misinterpreted. We see swellings on the chest-wall, generally on the anterior side. There is some fluctuation, but no redness or tenderness for many weeks. Eventually they rupture or are incised. They then discharge pus and finally a bloody, watery secretion. These swellings are called cold abscesses, tuberculosis of the ribs, and necrosis of the chest-wall. Stereoscopic radiograms should be taken in each of these cases. One generally finds the shadow of a localized pleurisy in the region of the swelling. Operation performed as an excision or dissection reveals a minute fistulous opening between two ribs leading to the outer surface of the parietal pleura. The ribs are almost never necrosed. It is often impossible to find either bacilli or tuberculous tissue. Nevertheless, the conduct of the lesion in every way resembles that of a tuberculous process.

Drainage alone in these cases has no curative effect, and excision of the abscessed area alone is likewise inadequate. However—and here the internist's coöperation is imperative—free drainage or excision, plus the maintenance of the hygiene advised for tuberculosis, is the sole source of success. Either one is valueless alone, but in combination the healing of an otherwise chronic discharging focus may be effected. In other words, the treatment of the case as one primarily of tuberculous pleurisy, which time will prove to be the basis of such lesions, in conjunction with free abscess drainage, is the treatment of choice.

There are other swellings on the chest-wall adherent to the ribs. These are tumors, either primary in the ribs and cartilages or extending to the tissues of the chest-wall from the pleura or mediastinum, rarely from the lungs. Some practitioners are accustomed to regard such tumors as inoperable. I suggest the following routine in these cases: Examine the stereoscopic radiogram. Evidences of underlying pleurisy will suggest the tuberculous abscess just mentioned; to all external appearances these abscesses are identical at the beginning with tumors. Examine the ribs with the roentgen ray; sometimes destruction of bone will confirm the diagnosis of malignant metastases. Study the mediastinal shadow. If there are lateral bulgings suggesting mediastinal tumor, the growth seen on the chest-wall is inoperable. Lymphosarcoma is the probable diagnosis; roentgen ray and radium are the only treatments. If, on the contrary, the intrathoracic roentgen-ray findings

'16—48

are negative, an operable tumor confined to the chest-wall may be confronting you. Myxochondrosarcoma of the ribs is the probable lesion. Radical removal of the tumor with the involved ribs may be performed with or without opening the underlying normal pleura. Pray do not consent to the dissection of such a growth from the ribs. It will recur. Permit only a total extirpation and see to it that despite assurances to the contrary by the surgeon, roentgen-ray therapy is employed *during* convalescence. If such operations are thorough, a lively reaction is to be expected on the chart. Bloody fluid accumulates in the *pleural* cavity. These developments are to be expected, but are almost universally withstood, and recovery ensues.

Of all swellings on the chest-wall, then, there are at least two types that are curable. A careful roentgenographic study of the case is imperative to determine the surgical possibilities.

In primary malignant disease of the lung itself surgery laments its incompetency. In the first or operable stages the symptoms are not sufficient to force the patient to seek medical advice. If roentgenograms are taken at the beginning of symptoms, a diffuse inoperable process may be detected. If a localized shadow is shown, it is misinterpreted generally as abscess or local pneumonitis. Expectant treatment in the hope of spontaneous drainage is employed. Meanwhile the disease progresses and at a late hour the cachexia of the patient reveals the probable diagnosis.

The removal of an early localized malignant tumor of the lung is surgically possible; but we cannot expect the internist to diagnose such tumors at the early stage. We, therefore, urge you to retaliate by ridiculing our unwillingness to perform exploratory operations within the chest as within the abdomen for diagnosis and for the determination of operability. The technic of such exploration has been perfected and yet it is not done. An exploratory thoracotomy should be a safe performance. Nothing will so promptly force us to more frequent explorations than the demands of our consulting internists.

The distressing predicament of persons with esophageal obstruction from carcinoma is a familiar picture. With the roentgen ray and esophagoscope you make the diagnosis. Despite the recent admirable studies and investigations, the general surgeon seeks to avoid an operative fatality. In view of our present knowledge and results, we would again assure you of our conservatism. We are devoted essentially to seeking the maintenance of nutrition by early gastrostomy; second,

we are learning to sidetrack the esophageal constriction, at the same time maintaining for the patient the consoling function of swallowing food. The esophagus is brought to the surface at some point above the stricture. A new esophagus is manufactured from the greater curvature of the stomach and brought subcutaneously to the upper thoracic region in close approximation to the presenting proximal end. The two are sometimes successfully connected either by suture or tubing. Then, and not until then, is intrathoracic extirpation of the esophageal cancer to be considered. Radium and the roentgen ray are first to be employed, but within a few years more successful extirpation may be recorded. In consulting with a patient thus afflicted the internist is urged to bear in mind the value of early gastrostomy, the recent successes in intrathoracic esophagoplastic surgery, and the possible value of intra-esophageal radium and extrathoracic roentgen therapy.

My title is the present status of the surgery of thoracic disease. He must indeed be an optimist who reads this story with any considerable enthusiasm as to the contributions which surgery at present affords. Should this paper be followed by an address detailing the results of expectant and medicinal treatment, you then would have listened to two sad stories instead of one. In view, therefore, of our individual incompetency, is it not imperative that our energies should be applied co-operatively that the much neglected thoracic region may become the scene of greater accomplishments?

THE SURGERY OF BRONCHIECTASIS, INCLUDING A REPORT OF FIVE COMPLETE RESECTIONS OF THE LOWER LOBE OF THE LUNG WITH ONE DEATH *

SAMUEL ROBINSON

Bronchiectasis is a chronic, loathsome disease, generally regarded as incurable. The expectoration is disgustingly profuse; consequently the afflicted loses employment, shuns society, becomes a recluse, and not infrequently resorts to dissipation. He is pale and a trifle cyanotic. His fingers and toes are clubbed. He labors with early fatigue. He coughs spasmodically, with varying persistency. Stooping, laughing, eating, hurrying, flood his trachea with pus and he retires, embarrassed, to drain himself of abundant sputum. In winter he is periodically ill with severe "colds," sometimes with bronchopneumonia, nor does the mildness of summer rid him of chronic cough. He may live many years, till cerebral abscess, pneumonia, septicemia, amyloid disease, or hemorrhage happily ends his existence.

A patient with a certain type of bronchiectasis is apt to remark: "I have coughed all my life, ever since I had measles (or whooping-cough) when I was small." He may say: "They say I had typhoid pneumonia when I was four," or "Ten years ago I had the grip and I've coughed ever since." It is probable that bronchopneumonia incident to such infections as the above constitutes the pathology from which develops the chronic state of bronchiectasis.

A foreign body (Fig. 336) may produce bronchial ectases, again possibly through the interposition of bronchopneumonia.

Bronchitis, unrelieved, may be attended eventually by dilatation of the tubes.

Chronic abscess of the lung associated with a chronic pneumonic

lung lobe will develop a condition in which some dilatation may be present. The term "bronchiectasis" is frequently applied to such a state.

Fetal bronchiectasis is described as originating in lungs remaining atelectatic from birth.

Chronic pleurisy, chronic empyema, and chronic non-tuberculous

Fig. 331.—(125,410.) Cylindric bronchiectasis. Excised lower lobe. (Case 2.) Recovery.

Fig. 332.—(154,561.) Cylindric and saccular bronchiectasis. Excised lower lobe. (Case 4.) Recovery

lung infections are sometimes forerunners to ectases of the bronchi and bronchioles. This relation, however, is uncommon.

Tuberculosis rarely accompanies bronchiectasis. When both are present, the upper lobe is generally the one involved, a fact which would indicate that the tuberculous process is primary and the bronchiectasis a later development (McCrae and Funk).

Tracheobronchial lymph-glands may enlarge sufficiently partially to

obstruct a bronchus; likewise tumors of the mediastinum and lung. Chronic bronchopneumonia may then be followed by bronchiectasis.

Fig. 333.---(173,830.)   Cylindric and saccular bronchiectasis.   Excised lower lobe.   (Case 5.)   Recovery.
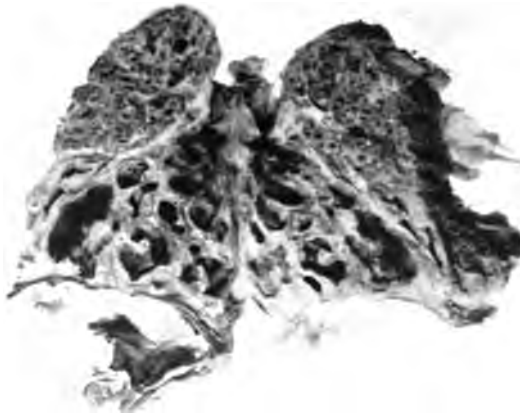
Fig. 334.— (A132,408.)   Saccular (ampullary) bronchiectasis.   Autopsy specimen of entire left lung.   Death followed drainage operation.

Syphilis may be a cause or at least an accompaniment. Positive Wassermanns are not infrequent in patients with bronchiectasis.

Unfortunately, because of its derivation, the term "bronchiectasis" may be applied to any bronchial dilatation, whether the latter be an incidental development or the underlying disease. As the clinical picture, the radiograph, and the pathologic specimen vary materially in the

Fig. 335.—(124,560.) Saccular bronchiectasis. Autopsy specimen of entire right lung. Death followed drainage operation.

different types of the disease, it is to be hoped we shall employ eventually more specific nomenclature to differentiate the several groups.

It is quite obvious from the specimens shown in Figs. 331, 332, 333, 334, 335, and 336 that the material forming the basis of this paper represents the exaggerated type of the disease.

It is absurd to regard the mere mechanical effect of coughing as the cause of bronchial dilatation of this idiopathic type. The bronchial mucosa becomes infected, and inflammation extends thence into the bronchial wall. We are necessarily ignorant of the pathology of this early stage when a bronchitis is becoming a bronchiectasis. If the usual primary bronchopneumonia has been survived, the patient lives on, at

Fig. 336.—(169,958.) Cylindric bronchiectasis following three-year retention of a foreign body (incisor tooth) designated by arrow. Death followed drainage operation.

least until the complete pathologic picture of the advanced disease is provided at autopsy or by lobe resection. Then we find cylindric ectases of the tubes, saccular, aneurysm-like dilatations of the walls, sclerosis of the parenchyma of the lung, and cord-like pleural adhesions. The lumen epithelium is cuboidal, the elastic fibers are scattered and

disconnected, the cartilages may be degenerated, the submucous vessels are dilated, and the adventitia has become a thick, fibrous, unyielding layer. We must assume for the present that the bronchial wall loses its tone from infiltrating infection. The diseased mucosa fills the lumen with purulent secretion, the expulsion of which, by coughing, forces the already weakened bronchial wall to dilate. The subsequent sclerosis of the peribronchial and interalveolar tissue may then, by contraction, drag the bronchial walls apart and still further pronounce the ectasis.

Fig. 337.—(125,410.) Roentgenogram, Case 2. Unilateral (right) basal cylindric bronchiectasis. Type suitable for excision.

I must omit here the details of diagnosis. The stethoscope contributes little; the sputum findings are by no means conclusive. The history, however, is most significant, and the x-ray, to say the least, confirmative. When clinically the case is probably one of bronchiectasis, the x-ray rarely fails to reveal both its presence and its distribution (Figs. 337, 338, 339, 340, and 342). When, however, in the beginning, differen-

tiation between chronic bronchitis and bronchiectasis is difficult, the roentgenologist is likewise doubtful. Furthermore, in cases of advanced and extensive ectasis with fibrosis the radiographic shadow may be homogeneously opaque (Fig. 341), atypical, and, therefore, not distinguishable from that produced by various other lesions.

Fig. 338.—(154,561.) Roentgenogram, Case 4. Unilateral basal cylindric and saccular bronchiectasis. Type suitable for excision.

EXPECTANT TREATMENT

The internist's treatment of this disease has consisted in hygiene, climatic influence, vaccines, postural drainage, medicated inhalations, and intratracheal injections. I have reviewed carefully the history of such therapies from the period of enthusiasm in England for creosote to the more recent claims for serum treatment. I find no evidence in either history or personal experience to dissuade me from the conviction that all non-surgical methods of treatment have failed to provide more than symptomatic relief of brief duration.

Collapse Therapy

This method of treatment is mentioned solely to emphasize its uselessness. It is not strange that the technical development of methods of collapsing the lung resulted in their employment in bronchiectasis. It would seem—and it is yet difficult to convince some surgeons to the contrary—that forcing the collapse of a bronchiectatic lobe would ob-

Fig. 339.—(156,113.) Right lower lobe bronchiectasis, operable.

literate the dilatation and sacculations, arrest secretion, and eventually heal the diseased portions. Ribs have, therefore, been resected to cave in the chest-wall over the infected area. Nitrogen gas has been injected (artificial pneumothorax) to produce lung collapse. An operative pneumothorax has been instituted, and the lower lobe separated from its adhesions, thus facilitating the shrinkage. Gauze packs have been placed within the pleural cavity, actually squeezing the bronchiectatic lobes. Extrapleural compression has been employed (Tuffier) to force the parietal pleura against the lung.

All these methods have failed to cure. No manner of compression is adequate to collapse the thick-walled, dilated bronchioles. The effect is as unproductive as would be the pressure of a sponge on a multitude of pipe-stems. The total lung volume is unquestionably diminished; the gross secretion is perceptibly reduced, and the patient is temporarily encouraged, but he is chagrined to find his permanent betterment trivial after being subjected to an operation of some gravity.

We are forced to conclude, therefore, that collapse therapy, though

Fig. 340.—(169,958.)   Bilateral bronchiectasis, inoperable.

of unquestionable value in certain types of pulmonary tuberculosis, is useless in cases of bronchiectasis.

LIGATION OF THE PULMONARY ARTERY

When the pulmonary arterial blood supply to a lobe of the lung is obstructed (Sauerbruch-Bruns), a shrinkage ensues. Microscopically, the interalveolar spaces are found to be occupied by an overgrowth of connective tissue resembling a fibrosis. The alveoli are consequently compressed and cease to functionate.

It was surmised, from these experimental findings, that such an operation might be curative in bronchiectasis. Again we are skeptical as to the future of this therapy in the type of bronchiectasis with which this paper deals. The pathologic changes are too far advanced to be rendered symptomless by arterial ligation. If applied in the incipient stage, such therapy might well be of definite value.

Fig. 341.—(124,560.) Roentgenogram: Advanced bronchiectasis with sclerosis. Cavities all obscured. Same case as that shown in Fig. 335.

PNEUMOTOMY—DRAINAGE OPERATION

It might appear to be an oversight were pneumotomy omitted in this discussion; nevertheless, it is not entitled to a place in the therapy of bronchiectasis. Drainage is yet persistently attempted, because of the traditional confusion between bronchiectasis and abscess of the lung; also because of the prevailing conviction, often difficult to overcome, that a pint of sputum must represent a large abscess cavity. Abundant sputum may come from cylindrically dilated bronchioles, presenting not even minute cavitations; it may arise from 20 or 30 sacculations not larger than a lima-bean (Figs. 334, 335); or it may be expelled from

three or four cavities, each 3 to 4 cm. in diameter.   Obviously, the drain-
age of such cavities must be of little avail because of the immediate prox-
imity of others.   Bronchiectatic cavities are rarely confluent; the sur-
gical opening of one does not necessarily mean the drainage of several.
Yet one may read of patients cured by such operation—many isolated
cases and sometimes groups of two or three.   Careful analysis of these
provokes suspicion that the operator may have been dealing with ab-
scess, rather than true bronchiectasis, and one is often left in a quandary

Fig. 342.—(57,973.)   Bilateral bronchiectasis, inoperable.

as to the late results.   Mosler collected the reports of 8 cases, and
though eager to prove that a drainage operation is curative, his interpre-
tation is open to dispute.

A true conception of the pathologic anatomy of bronchiectasis will
not permit of any faith in the effectiveness of drainage operations.   I
have attempted this in three cases, with direful results; autopsy only
exposed the absurdity of my plan of attack (Figs. 334, 335, and 336).
It is in the advanced septic cases, with involvement of most of one lung,
and in which excision is out of the question, that one is tempted to drain

in the hope of relieving toxemia. To enter the lung and "strike pus" seems at the moment gratifying. However, wound drainage as compared to mouth drainage is absurdly trifling. The patient's equilibrium, despite chronic sepsis, is upset. A negative phase is apt to follow, to which both heart and kidneys may succumb. Hemorrhage, slow but constant, is not an uncommon sequel which is apt to defy attempts at control.

·PNEUMECTOMY

I believe that there is but one curative treatment of true bronchiectasis—excision of the diseased lung tissue. The group of suitable cases, however, is small. A young adult with a basal process confined to one lower lobe; with profuse sputum, offensive but not fetid; with slight, if any, rise in temperature; with loss of weight, but without emaciation; with a normal heart and properly functionating kidneys—this is the type of person in whom lung resection, properly executed, is attended with good chance of cure. It matters little whether the disease is of the cylindric, ampullary, or large-cavity type, provided the general condition of the person is as specified. Not more than one in every ten cases of bronchiectasis entering a hospital clinic represents this favorable type. The remaining nine are unsuitable; one may be a rachitic child with low resistance; several may have extensive involvement of both lungs; another, a local process in an inaccessible part of the upper lobe; another, nephritis; and the remainder may be poor surgical risks because of extensive peribronchial disease, secondary infection, and gross cavitation.

As time goes on the definition of a suitable case for excision will be less specific. Childhood, and even infancy, may be excluded from the contraindications. In cases in which the disease involves both bases it is not impossible that excision may be performed on one side and subsequently on the other. Moreover, eventually the technic may be so abbreviated that even septic persons with complications may be regarded as suitable risks.

LUNG-LOBE RESECTION

The problem as to the necessity of dividing lung-lobe resection into two or more stages may long remain unsettled. The successes in animal experimentation are perhaps misleading. The removal of a lung lobe from the normal dog in one clean operation without drainage is simple to the extreme. The insult to respiration and pulmonary circula-

tion during operation is obviated by apparatus. The tight primary closure of the chest prevents postoperative disturbances in the remaining lung function and in the heart action. Lung infection is not a danger.

In man with diseased lungs and pleura the same one-stage lobe-resection has often been attempted. The mortality is at least 90 per cent. The operation itself is generally withstood with and without apparatus, but difficulties are apt to arise within twelve hours. The remaining lung functionates badly. The air exchange is insufficient. A "fluttering mediastinum" may be responsible, though probably not. The pulmonary circulation is upset; the right heart is overworked; toxins are absorbed; death may follow; and vaguely we conclude that the alveolar carbon dioxid content has been increased for lack of proper breathing, and the oxygen content of the blood lowered for lack of proper capillary circulation in the lungs. Be this pathologic complex what it may, it is now a familiar and gruesome picture in thoracic surgery.[*]

The fact that an occasional success has attended this one-stage lobe resection in man is not an argument that it should yet become the chosen method. It were better first to produce thoracic pathology in animals and study methods of overcoming it.

At present writing it appears to be safer and saner to divide lobe-resection operations into more than one stage. The thoracic cavity seems to prefer gradually to accustom itself to new conditions. The history of successful lobe amputation is instructive. Until recently excision accidentally occurred as the final operation of a series. Those preceding were performed for drainage of a supposed abscess. The lung was contracted; a subsequent empyema had been drained. "Plastics" for cure of the empyema had produced chest-wall collapse. The lung disease having meanwhile continued, a shrunken lobe was "cut away" as a final exploit. Thus have been recorded lobe amputations which were never intended when the preliminaries were performed. Nor did the operators realize perhaps that the preliminaries were responsible for the success of the amputation.

Probably the secret of success in the several-stage method lies in the fact that almost any operation on the thorax which opens or even exposes the pleura over a considerable area results in the formation of adhesions. When the pleura is opened in bronchiectasis, the diseased lobe in-

[*] It should be emphasized that the dangers associated with a one-stage lobe resection are by no means equally threatening in excisions of a portion of a lobe. Such excisions may be done in one stage.

variably is found adherent to the diaphragm, pericardium, and basal parietes. If, before such adhesions are entirely separated, an interval of time is allowed before the lobe is amputated, the normal lung tissue may be made to adhere. The mediastinum thickens and becomes less mobile. The diaphragm takes a new and higher position. The chest-wall contracts. The lung of the sound side learns of its vicarious duties. The pulmonary circulation gradually adapts itself to a less inflated and less mobile lung, and becomes accustomed to the gradual loss of the negative intrathoracic pressure upon which it physiologically leans.

With these adjustments first accomplished, subsequent amputation becomes less a disturber of the peace.

LOWER-LOBE RESECTION (TWO-THREE-STAGE OPERATION)

First Stage

Immediately before entering the operating room the patient should lie for an hour on a bed the foot of which is elevated. Coughing is then aggravated by the secretions which gravitate to the trachea, and the bronchial tree is at least partially emptied. Ether should be given by the drop method. An amount adequate to keep the patient in position is unfortunately sufficient also to lessen bronchial reflexes and to prevent coughing. Thus is permitted the accumulation, at and above the bronchial bifurcation, of the ever-present profuse bronchial secretion. Marked cyanosis results and persists. At frequent intervals the anesthesia should be "light" enough to awaken a cough, which alone, without expectoration, will clear the bifurcation sufficiently to admit air to the sound lung. In this manner the cyanosis may be lessened. At best the appearance of the patient is bad, such as in most operations would be attended with other alarming symptoms.

Tracheobronchial Aspiration.—On three occasions I have introduced the tracheal tube and have applied suction to it intermittently with a motor-driven aspirating outfit. Ether, given as usual with the mask, is inhaled around the tube. This suction mechanism disposes of much secretion and modifies the cyanosis. If one cannot promptly perform intratracheal intubation, the tube may be put through the nose to the pharynx, from which the suction device will remove the pus which wells up from the trachea. This intrapharyngeal aspiration, however, fails to remove the flooding at the bifurcation, where relief is most needed. The time used in providing for removal of secretion is well expended.

'16—49

Intratracheal Insufflation—Differential Pressure.—I regard as super-
fluous the employment of artificial aids to respiration during the two-
stage operation of lobectomy for bronchiectasis. Neither insufflation

Fig. 343.—Lower lobe excision in two stages: *a*, Crescentic incision; *b*, Stage 1: Thoracic window made.
Exposure of parietal pleura favors adhesion and anchorage of the upper lobe.

nor differential pressure was used in any of the five cases herein
reported.

Incision.—The incision is crescentic, with its convexity downward
(Fig. 343, *a*); starting at the level of the fifth rib, two inches from the

vertebral column, it crosses the eighth rib in the scapular line, and terminates at the level of the sixth rib in the mammary line.

The skin and fat are dissected upward from the muscle for an inch. Vessels are clamped and tied.   The latissimus muscle-fibers are separated vertically to admit long-bladed curved muscle clamps, which are applied in series above and below in the direction of the sternum and again toward the vertebral end of the wound.   The muscle-fibers are then divided transversely between the clamps.

A wet "salt square" is then applied to the edge of the skin-and-muscle flap, the clamps being wrapped within it.   The second assistant, standing by the patient's shoulder, retracts the flap and elevates the inferior angle of the scapula (Fig. 343).   Meanwhile the intercostal branches entering the muscle are clamped and tied.

The field thus exposed should permit the subperiosteal resection of the seventh, eighth, and ninth ribs from their angles to the anterior axillary line.   The intercostal bundles are then ligated and removed (Fig. 343, b).

Scapular retraction is omitted.   The muscle clamps are all removed, and a continuous locking catgut stitch is taken along the upper and lower cut muscle edges.

This stitch is solely for hemostasis; the muscle ends are not stitched together.   It is difficult to apply the locking hemostatic stitch at the beginning, before dividing the muscles.

The skin is now closed tight with figure-of-8 tension silkworm-gut sutures and a running horsehair stitch.

A graded compression pad made of folded gauze is applied to support the area of chest-wall denuded of ribs.   Three adhesive straps (2 inches in width) are placed to render the pad an effective buttress.   The usual dressing is applied, with more straps overriding the sternum and spine.

While generally such an operation is not followed by symptoms of shock, considerable blood-loss is inevitable, and the patient is in no condition to bear the added insult of pleurotomy and handling of the lung.

Much has been accomplished, however, by this first stage.   The thoracic window has been made ready to open.   The chest-wall collapse necessary for the subsequent obliteration of the space left after amputation of the lower lobe is provided.   Something has been learned of the patient's resistance to surgical trauma, of his tolerance of anesthesia,

and of the amount of flooding by tracheal secretion that is to be managed in his particular case.

The sole danger after the first stage is undue retention of purulent secretion. Coughing is painful; the expulsion of sputum, more so. The vis a tergo provided by the chest-wall in expulsion coughing is reduced by the operative defect, though somewhat restored by the compression pad.

Postoperative treatment then should consist in: (1) Moderation in the use of morphin lest coughing be unduly withheld; (2) such periodic postural therapy as may aid in drainage of the bronchial tree; (3) constant renewal or tightening of the compression pad and supporting straps; (4) early sitting posture; and (5) an abundance of fresh air.

Second Stage

The interval prior to the second stage should be approximately a week in length. The power of expelling sputum should have been restored; all trace of shock should have disappeared; and the temperature should approach "normal."

The anesthesia, tracheobronchial aspiration, and other preliminaries are established as before.

The skin stitches are removed; the scapula and flaps retracted; and the pleura again inspected. It will be found that in the upper part of the exposed field there are new pleural adhesions anchoring the upper lobe. The lower lobe is still adherent at various places, now somewhat retracted and purple red in color. The pleura is opened wide at any point, whether adherent or not. There will be no particular change in respiration or pulse.

The separating of adhesions necessary to deliver the lower lobe is generally irksome. It is the difficult part of the operation. The lower lobe is generally bound to the diaphragm and costodiaphragmatic angle by tough, unyielding bands which may not yield under digital pressure (Fig. 344). If undue force is used in stripping, the lung surface will tear before the adhesion gives way. Some of these should be cut. It is well, therefore, to free the lobe first from all but its diaphragmatic attachments, so that if bleeding occurs during the separation of the latter, a clamp may be applied temporarily in the region of the lobe hilus. The interlobar fissure does not always provide a simple cleavage, nor is it advisable to employ too much force in this region lest the light adhesions be parted which by now should be holding the upper or middle lobes to the parietes. The pericardial surface is least troublesome of all.

If at any time during this process of liberating the lung lobe dis-
turbances in respiration occur, the U-shaped skin-and-muscle flap is
promptly swung down to cover the pleural defect. It is jammed against

Fig. 344.—Lower lobe excision. Stage 2: Thoracic window opened; shrunken lower lobe is freed from its tenacious diaphragmatic adhesions.

the chest-wall with the palm of the hand until towel clips are applied
bringing the skin edges together for a temporary air-tight closure.   The
stimulating effect of this procedure is almost immediate.   A slight nega-

tive pressure is restored to the operated chest during the inspiration: the upper lobe receives some air; the mediastinum is held in better position because of greater equality in the intrathoracic pressure of the two sides. Consequently the sound lung functionates better.*

In Cases 1, 2, and 4 it will be noted that the second stage was closed in the midst of this separating of cohesions. In Case 5, however, this performance was completed and amputation done at the same sitting. As one's familiarity with the "lay of the land" increases, the necessity of three stages is diminished, and yet *to stop the operation at the middle of the second stage and to defer the completion of adhesion-stripping and amputation to a third stage is a conservative measure not to be regretted and one which, in difficult cases, may save the patient from undue hemorrhage, shock, and carbon dioxid poisoning.*†

It is not until one has worked in the open pleural cavity with his patient persistently cyanotic (a necessary condition in etherized bronchiectatic patients) that he will realize the consolation to be gained from the knowledge that the operation may be safely stopped at any moment in the second stage.

If, however, the second stage progresses favorably, so that it may include amputation, at least one distinct advantage has been gained; namely, the patient will then have been rendered practically sputum-free and the postoperative convalescence will not be complicated by the retention of purulent secretion—the expectoration of which is even more difficult after the incompleted second stage of the operation than after the first.

AMPUTATION

If there has been no occasion to close the second stage prior to the complete delivery of the lower lobe, amputation is promptly performed as follows: A long curved clamp is applied to the root and closed to the last notch. The lobe is then amputated at least a half-inch distal to the clamp. The veins, arteries, and bronchi are then picked up separately and ligated with No. 2 chromic catgut. A mass ligature of kangaroo tendon or braided silk is then placed just proximal to the clamp and tied as the clamp is slowly released, the ligature being guided into the crushed area evacuated by the clamp. Not infrequently two clamps are

---

* The necessity for such interruption I have experienced but once in a lobe-excision operation. The respiration once stimulated thus did not falter again (Case 4).

† The division into three stages was unquestionably responsible for recovery in at least two of my earlier cases.

necessary safely to include the whole stump.   It is apparently an equally satisfactory method to leave the root clamps in situ and to remove them on the seventh day (Case 5, Fig. 345).

Fig. 345.—Lower lobe excision. Stage 2 (continued): Amputation of lobe; clamp to be substituted by mass ligature; additional ligatures to vessels in stump. Two clamps may be applied and left in situ without ligation.

during its liberation and hastens the anchoring of the upper and middle lobes in their new position by adhesions.

During the first twenty-four hours the wound and the gauze pack should not be disturbed, lest a wide-open pneumothorax further restrict the efficiency of breathing, and the vis a tergo to expulsive coughing be sacrificed. Nevertheless, the onset of hydrothorax must be assumed and provided for just as soon as it is evident that the patient can dispose of his sputum despite the reopening of the wound and the loss of chest-wall support. This time arrives between the third and seventh days. It is well first to open a half-inch of the wound and allow the effusion, which will have overflooded the pack, slowly to leak out. This will relieve the patient of an intrathoracic tension which is painful, and which must always be relieved before it becomes excessive. Gradually, then, on the following day, the removal of the pack is started and finally completed in two subsequent daily sittings. When the pack is entirely removed, it must be carefully replaced, a procedure which necessitates wide opening of the wound with retraction of its edges. A drop-light is essential for the inspection of the pleural space in order that every unoccupied portion may be refilled with gauze; otherwise an overlooked pleural pocket may produce a local empyema. Furthermore, new adhesions will form between the collapsed lobe and costal pleura at any point where the packing is not replaced. The dehydration coincident to the profuse secreting of the pleura becomes apparent in the patient's facies, causing a marked pallor which persists for several weeks.

One is astonished 'at the rapid obliteration of the new pleural space around the collapsed lobe. Although the discharge becomes purulent and the cavity to all appearances is an empyemic cavity, it lacks the proverbial stubbornness to obliteration of an empyemic cavity. On the contrary, the space is rapidly filled by elevation of the diaphragm, by partial mobilization of the mediastinum, and by "healthy" pleural granulations.

The management of the interval following the second stage in a three-stage lobectomy cannot be followed by rule or schedule. Certain dangers are to be obviated, certain steps are to be taken, but the indicated and opportune moment for each must depend on the progress of the particular case in hand.

I am convinced now that in the three-stage lobectomies included in the case reports an undue interval was permitted between the second and the third stages. Two or three weeks should be sufficient.

The third or amputation stage of the three-stage operation is no more nor less than the latter half of the second stage of the two-stage operation already described. The separating of adhesions is completed sufficiently to deliver the lower lobe, which is then amputated.

INTERCOSTAL LOBECTOMY

To open the thorax without the resection of ribs by the technic which Mikulicz and Sauerbruch first utilized in experimental surgery is unquestionably the ideal method. The intercostal incision, followed by rib spreading, together with the division of one or two ribs, permits a perfect exposure for any intrathoracic operation. Lobectomy through such an opening has been universally successful in animals.

Lilienthal reports five complete lobectomies by the intercostal route in man with two deaths. Certain other surgeons have had a 100 per cent. mortality with the same technic.

One is instinctively loath to adopt a technic associated with high mortality in the hands of competent technicians, when a different technic, though infinitely more laborious, has resulted in but one death in five cases.

It is fallacious to argue that a person with bronchiectasis is too wretched to live, and that a surgical death is a permissible hastening of his exitus. On the contrary, such an individual should not be made the subject of great operative risk, as in cases of malignant disease. As wretched as his existence may seem to others, the unfortunate afflicted with bronchiectasis would probably never submit to an intercostal one-stage lobectomy if he knew in advance the present mortality of such an operation. The 20 per cent. mortality of the two-three-stage rib-resection lobectomy stamps it today as an operation which may be conscientiously advised. Nevertheless, be this as it may, the total number of recorded cases is too small to warrant the conclusion that intercostal lobectomy may not yet become the operation of choice. It is conceivable that the eventually accepted technic may be a combination of the several stage advantages of the rib-resection lobectomy, with the technical advantages of the intercostal lobectomy. Further experience may develop a method by which the intercostal technic may be combined with the two-stage idea in such fashion that the added simplicity of the former, coupled with the protective physiologic effect of the latter, may provide a method more ideal than either alone.

The technic of intercostal lobectomy is, therefore, herein described,

together with a discussion of methods of obviating some of its chief
dangers in order that this paper may not fail to mention an operation
which, in some modified form, may become eventually the operation of
choice.

TECHNIC OF INTERCOSTAL LOBECTOMY

Some form of mechanical aid to the respiratory function is indicated
in this particular type of operation. Intratracheal insufflation, alter-
nating at opportune moments with tracheobronchial aspiration, may be
used. The employment of differential pressure is particularly indicated
in bronchiectasis cases because of the profuse secretions. However,
such apparatus is rarely available.

The incision follows the seventh or eighth intercostal spaces from the
rib-angles to the costochondral articulation. The skin and fat are
dissected away from the muscles for an inch above and below the in-
cision. The muscles are divided the length of the incision; the vessels
ligated. Both layers of intercostal muscles are cut a distance of 2
inches at the center of the wound, the parietal pleura being thus exposed.
The pleura is then nicked, air being allowed to enter slowly as the open-
ing is closed intermittently with the finger. As respiration adjusts itself
to the open pneumothorax, the intercostal muscles and pleura are divided
to the ends of the wound, care being taken that the cut is made midway
between the ribs to avoid injury to the intercostal vessels.

Again it is well to pause to note the effect of wide-open pneumo-
thorax on the particular patient in hand. A rib spreader is introduced.
If the ribs cannot be separated sufficiently to permit access to the
diaphragmatic and pericardial regions, the seventh rib is divided at the
anterior end of the incision; it may also be necessary similarly to divide
the eighth rib. The lower lobe is then separated from the adjoining
lobe, the diaphragm, costal pleura, and pericardium.

At the completion of this generally laborious task the patient's con-
dition may be questionable. If the cyanosis is marked or the pulse of
poor quality, the rib spreader should be removed, the ribs pressed to-
gether, and the skin-edges apposed with clamps or towel clips. Even if
such temporary closure is not air tight, the lung function is enhanced
and the right heart is relieved. In the absence of response to such
stimulation it may be well to close the wound and postpone amputation.

If the patient's condition warrants proceeding, the lobe is ligated and
amputated in the fashion described.

The spreader is removed and the wound closed promptly as follows: Pericostal sutures (Sauerbruch), previously prepared of strong silk threaded in long, half-curved, slender, round needles, are placed $1\frac{1}{2}$ inches apart. The two adjoining ribs, intercostal muscles, and pleural edges are inclosed in these stitches. Each pair of suture ends is caught in a separate clamp.

These clamps are held aloft by an assistant in such a manner as to tighten the sutures and approximate the ribs as the surgeon ties. Previous to the tying of the end suture the assistant relaxes the tension, and a closed clamp is wedged between the approximated ribs to permit the free in-and-out going of air. At the end of an expiratory movement (if no apparatus is being used) the clamp is suddenly withdrawn, the suture drawn taut and hastily tied.

When differential pressure is being employed, it is exaggerated at the final moment of closure. If an intratracheal insufflation is in action, the outflow of air around the tube is obstructed momentarily at the end of respiration by bilateral compression of the trachea.

Each of these maneuvers tends to reduce the volume of air remaining in the opened half of the thoracic cavity, and consequently partially to inflate the lung. In the first instance (without apparatus) the chest-wall at the end of expiration collapses upon the lung. In the latter instance (when positive or negative pressure apparatus are in use) the lung is inflated at the moment of closure, the air thus being driven out of the cavity between the jaws of the opened clamp. In intratracheal insufflation a sudden obstruction to the air-outflow likewise inflates the lung.

When the last pericostal stitch has been tied by the method described, the divided chest-wall muscles are brought together with a running cat-gut stitch. As it is important that the muscle approximation should be made strong, it is well to interrupt the continuous stitch with ties at three points in its course. The skin is closed with a running silk stitch. The first few layers of gauze in the dressing should be held snugly to the wound by a strip of adhesive half encircling the thorax. The "closure in layers" tends to seal any leakage which may occur between the pericostal ligatures. Pressure to the dressing prevents hematomas which might separate the layers and destroy their hermetic sealing effect.

To restore the remaining lobes of the lung to a state of at least partial inflation at the end of the operation is to restore also part of their function. Not because inflation, as such, is of value, but rather because inflation is visible evidence that the intrathoracic pressure, which was

atmospheric during the operation, has been converted into a negative pressure at the close of operation. Without such negative pressure the lung of the operated side cannot functionate adequately.

Nor would the loss of the function of one lung alone be disastrous necessarily, were it not for the fact that in contrast to the normal negative intrapleural pressure of the sound side the lack of negative pressure in the diseased cavity which prevents the inflation of the diseased lung also permits a slumping of the mediastinal partition toward the sound side at inspiration and thus prevents the filling of the otherwise undisturbed lung. At expiration the mediastinum balloons toward the wounded half of the thorax. The sound lung, therefore, is not emptied of its gaseous waste product (CO_2).

Lilienthal applies a fixation ligation to the stump of the lobe. This is brought into the wound, drawn tight, and fixed.

The greater the oxygenating power of the lung, the less hectic will be the first twelve hours after the operation. Hence the importance of primary tight closure of the chest, even though its reopening be subsequently imperative.

Again stress is laid on the maintenance of proper breathing because the circulatory equilibrium is definitely dependent on it. Heart stimulants may appear to improve conditions, but when the respiratory compensation is broken, cardiac and circulatory disturbances must follow sooner or later.

The relation of pulmonary blood-pressure to lung inflation has been the subject of much dispute and some experimentation. The amounts of blood contained in an inflated lung and in a collapsed lung have been measured and compared. My own experimental conclusions in this regard have agreed with those of certain observers and differed from those of others. By means of a long cannula introduced through an opening in the internal jugular vein to the right auricle, and between the tricuspid valve to the right ventricle, I recorded the pulmonary blood-pressure. A cannula in the left carotid artery recorded simultaneously the general blood-pressure. The respiratory excursion also appeared on the kymograph tracing.

One pleural cavity was then opened. Both blood-pressures remained unchanged until the opening was enlarged, whereupon the lung collapse increased and the pulmonary blood-pressure declined. The fall in blood-pressure was synchronous with and proportionate to the onset of dyspnea. As the respiratory embarrassment was overcome and the lung reinflated by artificial means (positive pressure), the pulmonary

blood-pressure returned to normal. Had the same experiment been performed with the use of intratracheal insufflation to restore the respiratory equilibrium, the blood-pressure would doubtless have returned similarly to normal. Insufflation will maintain oxygenation without inflation—from which we must infer that the fall in pulmonary blood-pressure incident to wide-open pneumothorax in a dog is not due to the lung collapse per se, but rather to an extensive reduction in its function of oxygenation.

In other words, the quantity of blood in the collapsed lung, be it increased or decreased, probably has little to do with the changes in heart action following wide-open pneumothorax, provided the proper air exchange is maintained artificially. The slowing of the pulse and lowered pulmonary blood-pressure accompanying the dyspnea associated with wide-open, uncompensated pneumothorax may result from the stimulation of the cardiac inhibitory center by an excess of carbon dioxid. The actual relation of the circulatory to the respiratory functions in the presence of an open thorax is an unsettled problem in pathologic physiology.

DRAINAGE IN THE ONE-STAGE LOBECTOMY

The bronchial stump is a source of infection. A suitable culture-medium is provided by the hemorrhagic effusion which collects in the pleural space after operation. There is necrotic tissue both in the bronchial stump and in the stumps of adhesion bands which were cut away during the liberation of the lobe. All factors favor the progress of pleural infection.

Nevertheless, in the first twenty-four hours of convalescence the suction of the chest-wall is imperative. To destroy this by the addition of an open drainage is to sacrifice one of the chief promoters of recovery. It is well, therefore, before closing the intercostal stitch, to make a one-½-inch incision in the posterior axillary line overlying the intercostal space, which the intrathoracic guiding of the finger indicates as corresponding to the very bottom of the pleural space. An opening is then made from the incision through all the chest-wall tissues into the cavity. Through this a ¼-inch rubber tube is passed, which projects 2 inches into the space. Two silkworm-gut stitches are taken to approximate the skin closely about the tube, *which is corked or doubled over and tied or clamped*. The intercostal thoracic wound is then closed as described. A spigot, as it were, is this constructed, which may be opened with suction applied as occasion arises. If the lung collapse is later extreme, the intrathoracic pressure may be rendered negative by sucking the

pleural air out by this tube; simultaneously such fluid as may be present will be withdrawn.

If untoward symptoms develop a few hours after operation, effective restoratives are often sought in vain. The combined circulatory and respiratory embarrassments are woefully unresponsive to stimulation. For labored breathing a sitting posture, fresh air, and oxygen are helpful. For labored heart action, irregular and compressible pulse and low blood-pressure, caffein, camphorated oil, digitalis, proctoclysis, and hypodermoclysis should be administered.

Conclusions

1. Advanced bronchiectasis cannot be cured by medications, inhalations, intratracheal injections, intratracheal irrigations, climatotherapy, or vaccines.

2. Collapse therapy, produced either by nitrogen artificial pneumothorax or by surgical measures, is not curative.

3. Pulmonary arterial ligation is of more definite value as a preparation for lobectomy than as a curative measure per se.

4. Excision of the diseased portion of one lung is the only curative treatment of advanced bronchiectasis.

5. In the present status of the development of thoracic surgery lung resections should be performed in a two- or three-stage operation. The several stage operation of the rib resection type has been attended in the writer's experience with a 20 per cent. mortality.

6. The operation of intercostal lobectomy has distinct technical advantages. When performed in one stage, an undue risk of life is incurred. The physiologic advantages of the several stage technic may yet be successfully combined with the technical advantages of the intercostal exposure.

Case Reports

CASE 1 (See Ann. Surg., 1912, lv, 512–529. Included in this series by courtesy of the Massachusetts Hospital).—J. R. C., man aged thirty-six years, dredgeman. Lues nineteen years previously; two years of treatment. Cough for two years. Twenty months ago a period of dyspnea. Sixteen months ago "took cold"; fever, chills, dyspnea, night-sweats. Cough increased in the past fourteen months and was accompanied by thin, purulent sputum. Fourteen months ago, 55 ounces of "fluid" was aspirated from the chest, with some relief of the dyspnea.

December, 1908: Left chest: Flatness; absence of fremitus and

breath-sounds from fifth to seventh ribs anteriorly, and below the inferior scapular angle posteriorly. Right chest normal. Weight, 148 pounds; temperature, 98.6° F.; pulse, 90; leukocytes, 12,000. Sputum greenish, mucopurulent. Influenza bacilli; also a few pneumococci. No tubercle bacilli.

January 28, 1909: Pneumotomy (W. M. C.). Lung grayish in color and of tough consistence. Section removed with considerable hemorrhage. Pathologist's report: Lung tissue more or less solidified. Diagnosis: Chronic bronchopneumonia.

May, 1909: Rib-resection for drainage of empyema following pneumotomy.

October 18, 1909: Since last operation patient has had two exacerbations, with high fever and leukocytosis. Discharge now profuse from empyema wound. General condition improved.

Lobectomy (S. R.)—*First stage:* Anesthesia: ether, anesthol, and oxygen. A curved incision was made, with its convexity upward to include the scars of previous operations and the drainage wound. The muscle-and-skin flap was reflected downward; posterior ends of the ribs previously excised were removed sufficiently to admit the hand freely into the pleural cavity. The adhesions were extensive, preventing any indications of embarrassed respiration. Both upper and lower lobes were separated from the parietes with considerable difficulty and some bleeding. The adhesions in the fissure between the upper and lower lobes were also broken up.

Although the patient's condition was not alarming, it seemed advisable to complete the excision of the lower lobe at a second-stage operation. The entire lung was packed away from the parietal pleura, except at the apex, with handkerchief gauze. The lower lobe appeared to be of firmer consistency than the upper, although the latter was firmer than normal. The patient recovered from the preliminary operation during the following thirteen days, in which time the original gauze packing was not disturbed.

November 1, 1909: *Second stage:* Anesthetic: ether, anesthol, and oxygen. The incision of the last operation was lengthened to 10 inches. More of the eighth and ninth ribs was removed, permitting free access to the entire lower half of the chest-cavity. Removal of the gauze exposed the lower lobe free from adhesions. The lower lobe was then clamped 1½ inches from its root, and amputation performed distal to the clamp. The clamp then slipped from the unyielding lung tissues, permitting profuse hemorrhage from several points in the stump, together with leakage of air through exposed bronchi. The large vessels were clamped separately, and a mass-braided silk ligature was applied around the root of the lower lobe. The patient's condition was somewhat threatening. A large gauze pack was inserted into the pleural cavity around the amputation stump. The skin-and-muscle flap was

'16—50

only partially replaced with through-and-through silk sutures. The convalescence from the second operation was surprisingly good.

Fourth day after operation: Patient subjectively in better condition than for many months.

Eighth day after operation: Silk stay suture and gauze removed without hemorrhage.

Tenth day: Patient out-of-doors in wheel-chair. Sleeping well.

Seventeenth day: Wound-cavity visible and clean, with no sloughing; patient walking.

December 7, 1909: Evidences of bronchial leakage in the stump disclosed by whistling noise during coughing. Coughing since operation has been slight up to this time. No sputum.

June 23, 1911: During the past year and a half the patient's general condition has been distinctly better than for the past four years. The skin-flaps left unsutured have retracted into the exposed cavity and become adherent in better position than if they had been sutured to bridge the cavity. New skin has extended inward from the flaps sufficiently to cover the base of the cavity, with the exception of two square inches, in the midst of which are four small bronchial fistulas. Exploring these fistulas with a probe causes a reflex spasm of coughing, during which the diaphragm from below and the mediastinum and the heart from within bulge prominently. There is a slight mucopurulent discharge from these fistulas, but the reflex cough is not accompanied by sputum.

July 7, 1911: Plastic operation for closure of fistulas only partially successful.

1913 (Four years after lobectomy). A report was received at the Massachusetts General Hospital that the patient had died in New Brunswick of pneumonia. The details of death were never obtained.

CASE 2 (125,410) (Cylindric and saccular bronchiectasis of lower lobe, Figs. 331, 337, and 347).—H. S., man, aged twenty-four years, waiter. Alcohol and tobacco used in excess. Lesion on penis eight months previously diagnosed by local physician as luetic. No history of "secondaries" obtained. Cough of ten years' duration, dating from an "abscess of the lung." At that time large quantities of pus were expectorated for six weeks. Following this the patient was in moderately good condition except for a slight cough. Four months before examination the cough became more aggravated and was accompanied by a recurrence of foul sputum. Some dyspnea was experienced at night, which was relieved by the evacuation of half a pint of pus. During the past month there have been slight fever and three to four sweats at night. Cough is constant during the day, with profuse expectoration. Some loss of weight. Lungs examined by auscultation: Marked dulness, diminished fremitus, and diminished breath-sounds at right base. "Signs of cavity." Many "squeaks" and râles heard over both sides of the chest; most marked over the right side, and possibly originating

entirely from it. Roentgenogram (stereoscopic): "Bronchiectasis on right, with multiple cavities at right base" (Fig. 337). Wassermann reaction negative. Sputum: *Gram stain:* Pneumococci, pus-cells. Micrococcus catarrhalis. *Blood-agar plates:* Pneumococci. No influenza bacilli.

March 17, 1915: Right lower lobe resection. *First stage:* Five inches of the seventh, eighth, and ninth ribs were resected. Pleura opened wide. The lower lobe was freed from its adhesions. Diaphragm adhesions were not resistant. In order to prevent complete collapse of the lung, the anterior border of the diaphragmatic surface of the lower lobe was sutured to the upper border of the thoracic window. A gauze pack was then placed in those portions of the pleural cavity not occupied

Fig. 346.—(Massachusetts General Hospital.) Case 1. Lower lobe excision one year after operation.

Fig. 347.—(125,410.) Lower lobe excision. Case 2. Two months after last operation. Pleural space not yet obliterated.

by the partly collapsed lung. The skin-and-muscle flap was sutured in place without drainage.

The patient was cyanotic both before and after the opening of the pleura, and remained so until coughing reflexes returned and the secretions which had collected in the trachea were expelled. Six days after the operation the stitches were removed and the gauze pack withdrawn. It was soaked in serum, some of which had escaped between the stitches. As the lower lobe suture had held, its diaphragmatic surface was readily accessible through the wound. The gauze pack was renewed daily. Two weeks after the operation six openings were made with a clamp in the under surface of the lower lobe as it presented in the wound, in the hope that at least some purulent secretion might escape and reduce the quantity of sputum which was now difficult to "raise." A temporary discharge followed through the fistulas thus produced, but with no ma-

terial relief to expectoration. In the following two weeks a septic condition developed, with fever, leukocytosis, and loss of weight. Examination of the wound revealed nothing. Examination of the chest was unsatisfactory because of the peculiarly altered conditions in the right pleural cavity. The left lung, however, appeared to be normal. Pus was obviously present, but there was no clue as to its location. Fortunately a new discharge from the anterior end of the wound disclosed a tract connecting with a walled-off portion of the pleural cavity adjacent to the mediastinum and pericardium.

April 16, 1915: Ether. Localized empyema drained and packed. A prompt recuperation followed, with gain in weight.

June 11, 1915: Lobectomy, *second stage:* The skin-and-muscle flaps were dissected upward. The two ribs next above those previously resected were removed from angle to mammary line. The lower lobe was then freed from all adhesions, including those to the parietes. The interlobar fissure was also spread open one-half of its extent. The operation was then brought to a close by the introduction of two gauze packs with which the lobe was "jacked up" away from all surfaces from which it had now been freed.

.The postponement of amputation in this case was not occasioned by any unfavorable change in the patient's condition. Considerable time had been consumed, however, and the fear that any accidental blood-loss during an amputation might not be withstood resulted in the decision to close the operation. The recovery from this stage was uninterrupted. The amount of sputum diminished only one-third after two months of actual compression of the diseased lobes within the pack, which was renewed daily. (This observation did much to destroy my faith in the curative effect of collapse therapy in advanced bronchiectasis.)

August 12, 1915: Lobectomy. The original field of operation was again freely exposed. No further rib resection was necessary to permit ready access to the lobe hilus, which was clamped and ligated en masse with kangaroo tendon. After amputation of the lobe the separate arterial, venous, and bronchial branches were ligated with catgut distal to the mass ligature. The emptied portion of the pleural cavity was then packed with gauze, and it was noted that the upper lobe was everywhere coherent to the parietes, which fact precluded the possibility of any further concealed pleural infection. Within one week the lobe-strings sloughed away, leaving two small fistulous openings. Within two weeks the cavity was "clean" and its walls granulating.

September, 1915: The diaphragm has rapidly elevated itself. Shrinkage of all the cavity diameters has occurred. The upper lobe has not contributed to the filling of the emptied pleural space. The wound is rapidly decreasing in size in all dimensions (Fig. 346).

January, 1915: The patient has been at home three months. He has gained 30 pounds in weight. He has had neither sputum nor cough for

four months. The wound is healed except at a small area in the new epithelium, where two open bronchial fistulas persist, and from which there is a very slight non-purulent discharge. These fistulas do not seem to concern the patient sufficiently to cause him to return for their repair.

December, 1916: The patient reports himself well and traveling with a show. He requests the ownership of the "lung in a bottle," that his demonstrations at the show may be even more profitable.

CASE 3 (130,276) (Chronic abscess of the lung, bronchiectasis, pneumonitis. Death from encapsulated empyema).—T. S., man aged twenty-three years, janitor.

This patient had had no illnesses previous to seven months before admission to the Clinic, at which time tonsillectomy was performed under general anesthesia three days after an acute attack of tonsillitis. The following night coughing commenced, with expectoration and throwing up of blood. Such bloody sputum continued for one week. During the following three months the blood disappeared from the purulent sputum, which continued in increasing quantities. For the past five months loss of strength persisted, with profuse expectoration in the early morning. The vomitus amounted to a half-pint in twenty-four hours. The sputum was generally brownish or gray.

Upon admission to the Mayo Clinic a clinical diagnosis was made of "abscess of the lung." The sputum was negative for tubercle and influenza bacilli. Pneumococci; Micrococcus catarrhalis; Diplococcus crassus.

Roentgenologist's report: Marked increase in density over lower two-thirds of left chest; probably old abscess in the anterior portion. Considerable retraction of pleura.

May 14, 1915: Exploratory thoracotomy. Four inches of the sixth, seventh, and eighth ribs were resected in the region of the inferior angle of the scapula. The pleura was opened wide. The lower lobe of lung was found to be adherent to the diaphragm and to the posterior distal pleura. Palpation of the lobe revealed no definite focus suggesting an abscess. It was assumed, therefore, that a chronic condition was present, in which a pneumonitis had developed around abscesses or in association with bronchiectasis. The adhesions to the diaphragm were separated, and the anterior border of the diaphragmatic surface of the lower lobe was sutured to the upper border of the thoracotomy wound. A note dictated at the time of operation reads, "thus exposing the under surface of the lower lobe for later exploration with instrument or cautery. Abscess left lung."

A large gauze pack was placed in the lower pleural cavity. The wound was closed tight. Subsequently I concluded that the necessary procedure in this case would be excision of the lower lobe, from which

decision I must needs regard this preliminary operation as the first stage
of lobectomy, though it was not intended as such.

The day after operation the pulse rose to 120, from which point it
fell gradually in the course of the following fifteen days.   On the seventh
day the temperature was 102° F., falling by lysis until the antemortem
rise again to 102° F.   The cough returned to its preoperative state,
with the expectoration of green, tenacious sputum.   There was increas-
ing loss of weight and strength.   Finally dyspnea developed.   The
gauze packs were changed daily after the third day.   Death occurred
on the fifteenth day.

Autopsy findings: Moderate degree of cylindric bronchiectasis.
Large chronic abscess in the lower left lobe.   *An acute left encapsulated
empyema not connecting with the operative wound.*   Acute purofibrinous
plastic pericarditis with effusion.

Death occurred in Case 3 from septicemia resulting from an un-
recognized encapsulated empyema occupying a portion of the pleural
cavity which was packed with gauze at the operation, but which was not
packed in the subsequent dressings.   It is conspicuous that this accident
occurred in three out of the five cases herein reported.   In two of these
the encapsulated area was searched for and discovered, the patients thus
being saved from a similar death.   This untoward complication is
emphasized as the most dangerous sequel to the several stage operation
—a sequel, nevertheless, which, if not avoided by careful packing, may
yet be overcome by detection of the area and drainage.

CASE 4 (154,561) (Saccular bronchiectasis of the lower lobe and of
the basal portion of the upper lobe, Figs. 332, 338, and 348).—B. L. P.,
aged twenty years, clerk.   Fourteen years previously the patient inhaled
one-half a plum-stone.   Four months later he developed a severe cough.
Six months later he "coughed up" the plum-stone.   Since that time
(thirteen years ago) the cough and expectoration of purulent material
have persisted.   Frequent colds.   Occasional night-sweats.   Sputum
rarely blood-streaked.

Physical findings: A pale and anemic but fairly well-nourished young
adult.   Fetid odor to breath.   Relative dulness over entire left chest,
particularly at the lower portion.   There were numerous loud, squeaking
râles at left base, with areas of tubular breathing.

Leukocytosis, 10,200.   Urine negative.   Roentgen findings: Marked
thickening and cavitation in the left base.   Thickened pleura at left
base.   Heart drawn to the left.   Diagnosis: Bronchiectasis.

Operation: Left lobectomy; · three stages.

April 16: *First stage:* Ether anesthesia: tracheobronchial aspiration.
Seven inches of sixth, seventh, and eighth ribs were resected in the in-
ferior scapular region.   The pleura was opened accidentally during the

rib resection. Pneumothorax was produced in the upper portion of pleural cavity. The lung was seen to be adherent below, but was not palpated. The skin-and-muscle flap was restored with silk sutures. No pack. Throughout the operation the patient was cyanotic from secretions in the trachea.

April 28: *Second stage:* Tracheobronchial aspiration. The original flap was raised and lengthened and six inches of two ribs above the wound were resected. The pleura was reopened high where the lung was not adherent. Pneumothorax caused no symptoms. The lung was adherent to the diaphragm and the lower costal pleura. All adhesions were separated except those to the adjacent lobe and to the pericardium. A gauze pack was placed to fill all vacancies, and over it the skin-and-muscle flaps were sutured for tight closure.

Fig. 348.—(154,561.) Lower lobe excision, Case 4. Two months after operation.

A profuse serous discharge leaked between the wound stitches on the third day. Temperature normal; pulse 120. The patient was out of bed on the fifth day.

May 16: Ether. Removal of pleural pack (two weeks after its introduction). Skin stitches gaping; pack presenting. The gauze was found soaked with serum, but not pus, and firmly adherent to the pleural surfaces. The pack was renewed.

May 24: Ether. Second renewal of pleural pack.

June 1 to August 4: Daily renewal of pack to pleural space, which gradually reduced itself to the size of a walnut.

August 5, 1916: *Third stage of lobectomy:* Original operative wound was widely exposed, necessitating removal of certain rib ends. The lower lobe was rapidly delivered, and a single large clamp applied to the lobe root. A mass silk ligature was applied proximal to the clamp and

drawn taut as the clamp was removed. The vessels and bronchial branches were ligated separately with catgut or silk, and a large gauze pack placed in the lower pleural space. The lower anterior portion of the upper lobe was noted to be of dark color, resembling that of the bronchiectatic lower lobe. It did not seem to be a fitting occasion for further lobectomy, and it was hoped that subsequent shrinkage might obliterate any process which might be present in the tongue of the upper lobe.

Bronchial leakage occurred with sloughing away of the stump on the seventh day. Through this fistula a purulent discharge was noted. There was complete absence of sputum except when a recumbent right lateral posture prevented fistulous drainage. Even then the quantity of sputum never exceeded two ounces in twenty-four hours.

December 25, 1916: The patient has regained his weight—he is no longer anemic. The wound is healed except for a minute fistulous opening now surrounded by skin, through which comes an offensive discharge. As long as this opening is patent there is absence of sputum. This man has now been advised to have a further resection of the portion of the upper lobe in which disease is apparent in the roentgenogram. Comparison of this recent roentgenogram with that taken previous to the first operation shows that the upper limit of the bronchiectatic cavitations has not changed, a fact proving that the upper lobe process was present in the beginning and has not since increased.

CASE 5 (173,830) (Saccular bronchiectasis, Fig. 333).—G. T., man aged twenty-six years, brakeman. Influenza eight years ago. Five years ago he began coughing. The sputum was not excessive, but was occasionally blood-streaked. It gradually increased in quantity and acquired a foul odor, until recently, when twice a day he raised half a cupful of yellowish, fetid sputum with such force that it frequently discharged through the nose. No chills, sweat, or fever, but frequent "colds."

Eight months previously a rib resection operation was performed over the lower left chest by a Toronto surgeon. No relief resulted. Clinical diagnosis: Bronchiectasis. Roentgen findings: Retraction of ribs in costophrenic angle. Increased density resembling fluid. Bronchi apparently dilated. Case could be one of bronchiectasis.

Operation: *Left lobectomy, two-stage operation.*

October 9, 1916: *First stage:* Original area operated on by the Toronto surgeon was exposed by elevation of a crescentic flap. The ends of four ribs were resected further for two inches anteriorly and posteriorly. The pleura was opened 1.5 inches during the separation of the old operative adhesions. The lower lobe was found adherent to the diaphragm. A part of the interlobar fissure was open. The patient was markedly cyanotic during the whole operation. The pulse was al-

ways good. Tracheobronchial aspiration not used. The skin-and-muscle flap was sutured tightly in place.

Six days after the operation difficulty in breathing developed, together with sense of pressure in the substernal region. There were fever and leukocytosis. Opening of the wound permitted the escape of serum, but the general septic condition was not altered. The fatal occurrence of an encapsulated empyema in Case 3 and the well-nigh disastrous similar occurrence in Case 2 led to the suspicion that following the operative pneumothorax the lung had not entirely reëxpanded, that this unoccupied pleural space, probably in the upper thorax, had filled with fluid, which, being retained, had become infected. A roentgenogram verified the suspicion, showing clearly an encapsulated hydropneumothorax at a higher level than the now open wound.

October 23, 1916: Under ether anesthesia exploration for encapsulated fluid. Adhesions of left lower lobe to diaphragm were separated without recovery of the fluid. The lower lobe was then separated from the outer wall, permitting the escape from above downward of a quart of thin, semipurulent, foul-smelling fluid. A large gauze pack was introduced. The patient's condition promptly improved.

November 1, 1916: *Second stage:* The wound was reopened. No further rib resection was necessary. The parietal pleura was found to be thickened 1/4 of an inch. The lower lobe was exposed at the level of the diaphragm. The lobe was then freed from all attachments with more rapidity than in the previous cases. Unusual bleeding resulted, the source of which was not discernible until a clamp was placed on the lobe hilus, at which moment all bleeding stopped, exposing areas in the lobe lacerated during its delivery. Two more clamps were applied to the root for security—the experiment being tried for the first time of trusting to the clamp-crushing for hemostasis, and for at least the usual degree of bronchial closure. Therefore no ligatures were applied. A large gauze pack was carefully placed, it being noted meanwhile that the upper lobe had no parietal adhesions because of the unfortunate occurrence of the localized pneumohydrothorax following the first-stage operation.

The clamp handles were tied together with silk. Seven days after the operation two clamps were removed. Two days later the third one was removed. The upper lobe lay almost completely collapsed against the posterior wall. A slight bronchial leakage which became apparent on the tenth day delivered a moderate amount of semipurulent secretion which has since gradually disappeared.

December 29, 1916: The patient was discharged from the hospital. In two months following the lobe amputation he has gradually regained strength, though considerable septic absorption occurred during the "cleaning up" of the cavity, from which sloughing fragments of visceral and parietal pleura have been thrown off. Today the entire cavity is clean and the parietal surface is covered with pink granulations. The

visceral pleura is thin and free from exudate. There is no cough or sputum by day. At night a reflex cough is probably occasioned by the passage of air through a minute fistulous opening which lies under the overhanging border of the collapsed upper lobe.

The temperature is normal, and the pulse steadily falling as the patient's general condition improves.

Within a few weeks a decortication of the visceral pleura of the upper lobe will be performed, in order to restore its function and if possible to obliterate the now much shrunken pleural space.

REFERENCES

Avery, O. T., and Lyall, H. W.: "Concerning Secondary Infection in Pulmonary Tuberculosis," Jour. Med. Research, 1913, xxvii, 111.

Bouchut, L., and Dujol: "Syphilis et dilatations bronchiques," Rev. de med., 1912, xxxii. 584–599.

Bourée, F.: "Contribution à l'étude de la pathogénie de la dilatation des bronches," Thèse de Paris, 1904–5, Michalon, Paris, 103 p.

Box, C. R.: "The Treatment of Bronchiectasis," Practitioner, 1906, lxxvi, 839 851. "Bronchiectasis in Childhood, with some Observations on the Condition Known as Honeycomb Lung," Lancet, 1907, i, 16–19.

Bruns, O., and Sauerbruch, F.: "Die künstlische Erzeugung von Lungenschrumpfung durch Unterbindung von Aesten der Pulmonalarterie," Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1911, xxiii, 343–350.

Chaplin, A.: "The Treatment of Bronchiectasis," Practitioner, 1906, lxxvii, 730–738.

Dallidet: "Anatomie pathologique et pathogénie de la dilatation des bronches," Thèse de Paris, 1881. Parent, 76 p.

Dazincourt, C.: "Des resultats de l'intervention chirurgicale dans les bronchiectasies," Paris, Steinheil, 1896, 78 p.

Ewart, W.: "The Treatment of Bronchiectasis and of Chronic Bronchial Affections by Posture and by Respiratory Exercises," Lancet, 1901, ii, 71–72.

Fleming, R. A., and Gibson, H. J. C.: "Two Cases of Bronchiectasis (Non-tuberculous) Treated with Autogenous Vaccines," Edinb. Med. Jour., 1915, xv, 197–201.

Godlee, R. J.: "Surgical Treatment of Pulmonary Cavities," Lancet, 1887, i, 457–459; 511; 667–670; 714–718.

Laennec, R. H. T.: "On Mediate Auscultation and on Diseases of the Heart and Lungs," London, 1846, Bailliere, 862 p.

Leach, E.: "Bronchiolectasis in Children, with Reference to the Condition Known as Honeycomb Lung from a Clinical Standpoint," Quarterly Jour. Med., 1908–9, ii, 251–260.

Lilienthal, H.: "The Therapeutics of Chronic Suppurative Bronchiectasis," Ann. Surg., 1916, lxiv, 8–33.

McCrae, T., and Funk, E. H.: "Bronchiectasis of Upper Lobes," Jour. Amer. Med. Assoc. 1916, lxvii, 1060–1066.

Meyer, W.: "Pneumotomy for Localized Bronchiectasis and Gangrene," Ann. Surg., 1913, lviii, 700–701.

Mosler, F.: "Ueber Lungen-Chirurgie," Wiesbaden, Bergman, 1883, 72 p.

Mumford, J. G., and Robinson, S.: "The Surgical Aspects of Bronchiectasis," Ann. Surg., 1914, lx, 29–35.

Robinson, S.: "Pneumectomy: its Possibilities. Report of a Case of Partial Lung Excision," Ann. Surg., 1912, lv, 513–529.

TUBERCULOSIS OF THE SPINE: END RESULTS OF OPERATIVE TREATMENT *

MELVIN S. HENDERSON

Since 1912, as a result of the original work of Albee[1] and Hibbs,[2] the attention of the medical profession, and to a large extent that of the laity, has been directed to the operative treatment of tuberculosis of the spine. Sufficient time has now elapsed to warrant a review of these methods of treatment, and it is with this object that I here report the condition of 81 patients so treated. In this connection it may not be out of place to mention the object of these two methods, their essential differences, and what we may reasonably expect of such procedures.

The Hibbs and Albee methods are similar in that each has as its object the establishment of a bony splint on the posterior surfaces of the diseased vertebras, thus preventing motion which is both painful and detrimental to healing. That this is possible by either method has been amply shown by Hibbs and Albee and other writers. Hibbs prefers to secure the fixation by an osteoplastic operation on the spinous process and the laminas of the vertebras, while Albee advocates the use of a transplant taken from the patient's own tibia and placed in a trough chiseled in the spinous processes and interspinous ligaments. Inasmuch as the two methods are so nearly alike in their basic principles their relative merits will not be discussed. Figs. 349 and 350 show the essential differences of the two methods. Both methods require an accurate and careful technic with perfect asepsis. If these are not provided, the operation in a great majority of cases will be a failure. Finally, and most important of all, it must be remembered that neither method is in any sense of the word a radical procedure. The location of the disease, surrounded as it is by most important structures, forbids the performance of a radical operation such as may be carried out for tuberculosis of the knee-joint. The purpose of the Hibbs and Albee operation is to place a bony

living brace to the spine and thus shorten the period of recumbency,
cast and brace wearing.

The proper selection of cases is essential. Debilitated patients and
those in which the disease is hopelessly advanced should not be subjected
to operation. This type should be observed and attempts made to in-
crease the resistance by careful conservative methods. If these patients
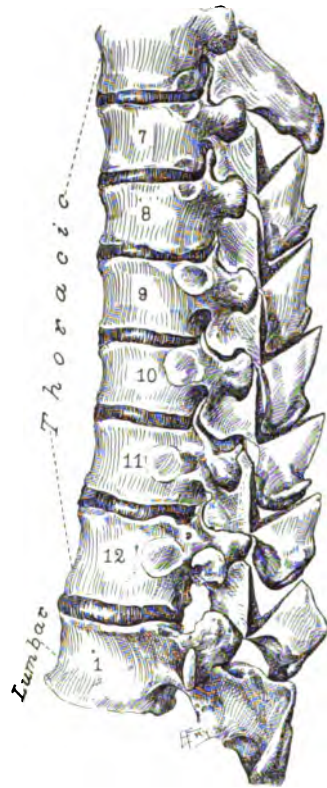
Fig. 349.—Hibbs' operation; fracturing the
spinous processes at their bases.
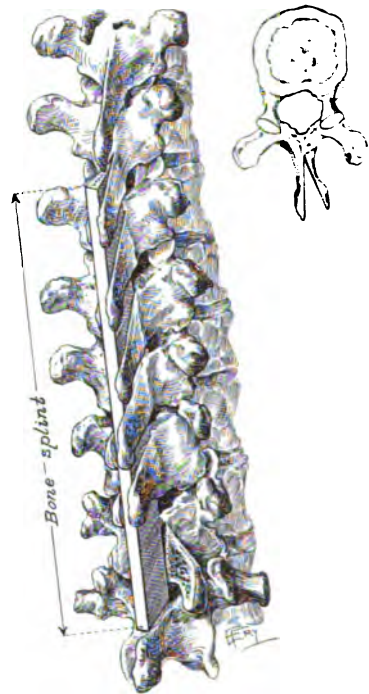
Fig. 350.—Albee operation. Transplant placed in
the split spinous processes.

do not respond to resting the spine by recumbency, it is not at all prob-
able that they will respond to operative procedures. Conditions of the
lung should be carefully ascertained by physical examination and cor-
roborated by the roentgen ray before operation on the spine, since pa-
tients with tuberculosis of the spine associated with pulmonary tubercu-
losis cannot justly be subjected to the same risk, as, for example, those
with tuberculosis of the knee associated with pulmonary tuberculosis.

In tuberculosis of the knee something approaching a complete extirpation of the diseased area can be performed, while in tuberculosis of the spine this is not possible. Accordingly, tuberculosis of the lungs must be proved healed or quiescent before the patient is subjected to an anesthetic.

For some unknown reason transplantation of bone is not so uniformly successful in children as it is in adults. By repeated x-ray examinations of the spine following transplantation of bone in children we have seen the graft gradually absorb so that there is no trace of it at the end of a year. The same observation also applies to osteoplastic operations. By this I do not mean to say that children should not be operated on, but that, because of the reasons stated, the question of operation should be weighed very carefully. Only 7 of the patients in the series of cases reported were under twelve years of age. Children can be very easily controlled on a Bradford or Thomas frame, and even when operation is performed, rest on one of these frames should be insisted on until the disease is known to be quiescent.

We see adult patients with tuberculosis of the spine who have had considerable destruction of bone, with resulting abscesses and sinuses, but in whom the skiagram shows there has been a coincident vigorous bone repair. Clinically such patients are not benefited by either of the operations under discussion for they already have what the operation is intended to produce, namely, ankylosis.

The diagnosis in tuberculosis of the spine is most often made too late, not infrequently when the patient himself calls the attention of the physician to the "lump" in the back. To get the most out of the Hibbs and Albee operations the patient should be operated on before deformity appears or at least before the deformity has reached any considerable size. When it is possible to place the graft in the spine without fracturing or bending it, the patient has a much better chance than when it is necessary to fracture the graft in order to accommodate it to the kyphos. It is somewhat difficult to fit the straight graft to the kyphos and even when skilfully done such fitting is certain to weaken the graft. The bone must usually be fractured in order to accommodate it to the curve, and there is always the chance that union of the fracture may not take place. Figs. 351 and 352 show two methods I have used to overcome this difficulty. Fig. 351 shows a V-shaped osteotomy performed at about one-third or one-fourth of the distance from each end of the graft. It is planned that the base of this V osteotomy shall be in the medullary

portion and the apex of the **V** carried almost through the cortex. The graft is then gently fractured at each osteotomy point, so that the break will be practically a greenstick fracture. The periosteum, being intact, prevents any separation of the fragments. Thus it is possible to accommodate the graft to the contour of the kyphos. The other method (Fig. 352) is to be used for patients having a pronounced kyphos, and consists of sawing the graft, which is usually about 7 inches long, into three pieces, and dividing each piece longitudinally. These can be
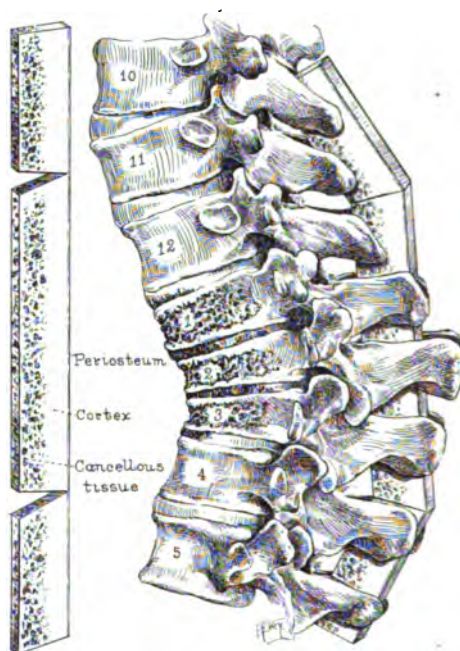
Fig. 351.—Method of fracturing graft to fit kyphos.

placed in the trough so that the ends of the short pieces are held in side-to-side apposition. Union will occur and a strong graft result.

Paraplegia due to the disease does not seem to be a contraindication to operation. I have had no occasion to operate on such a case, but good results following operations have been reported by others.

Our duty to our patients is not finished after the operation is completed. They must be kept recumbent until the bone transplant is firmly adherent to the spinous processes or the osteal flaps are united. Rest on a gas-pipe frame or stiff bed for at least a month is essential, and I am lately inclined to lengthen this period, varying it somewhat

according to the demands of the individual case. A well-fitting back brace should be provided for the ambulatory period, and patients should be instructed to wear this for one year after all active signs of disease have disappeared. They should live under the hygienic surroundings and have the tonic and sustaining treatment that are prescribed for patients with tuberculosis of the lungs. This treatment is controlled to a very
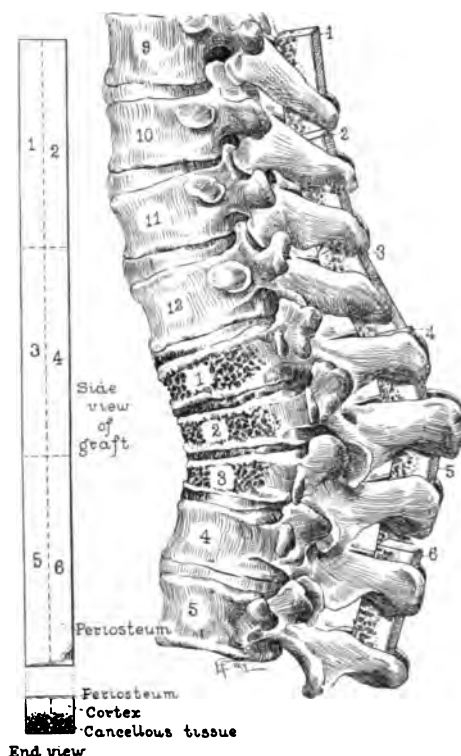
Fig. 352.—Method of accommodating graft to kyphos.

great extent by the social status of the individual, and unfortunately can be carried out often to only a limited extent.

In the Mayo Clinic, from July, 1912, to July, 1916, 274 cases of tuberculosis of the spine have been observed. Eighty-one cases were operated on—74 according to the method of Albee and 7 according to the method of Hibbs. Fifty-one of the patients were males and 30 females. The average age was twenty-five years, the oldest patient being fifty-three and the youngest two. Only seven were under twelve

years of age. The disease was located in the lumbar region in 34 instances, in the dorsal in 36, and in the dorsolumbar in 11. The average duration of symptoms was two and one-half years. There were no deaths due to the operation. Seven of the series are known to have died some time after the operation. These deaths will be discussed later. Three cases are too recent to report upon except to say that the operative convalescence has been uneventful. Five cannot be traced. Seventy-three cases, therefore, are the basis of our percentages.

The exact time at which patients who have suffered from tuberculosis of the spine are cured is difficult to state, even when we have them actually under observation. It is still more difficult to decide when the only means we have of judging is by letter. I have classified as cured those patients who say they have none of the pain they suffered before operation, who are able to go about without spinal support, and who have again taken their places in the every-day life of normal people. Our patients have been routinely advised to seek light occupations. This, of course, is not always possible, and not a few of them are now doing hard work as the only means by which they can procure a livelihood.

Thirty-one patients (42.4 per cent.) are cured. Some of them were able to return to work in six months, others not for three years, but the average returned between one and one and one-half years. Thirty-three patients (45.2 per cent.) are classified as relieved, though no doubt some of this group will go on to a cure when sufficient time has elapsed. Although there were no operative deaths, 7 of the 73 patients (9.5 per cent.) are known to have died later; 2 of these had been cured of the tuberculosis of the spine. One was a young man, aged twenty-three, who had had a Hibbs operation, aspiration of a huge psoas abscess, and injection with 10 per cent. iodoform emulsion. Following this treatment he gained 40 pounds, was apparently well, and resumed hard manual labor for one year. After a severe cold he had a persistent cough, and died within three months of acute miliary tuberculosis of the lungs. The other was a married woman, aged thirty-two, who made a perfect recovery following operation, only to die three years later of pulmonary tuberculosis. Four of the remaining five patients who died later of diffuse tuberculosis should not have been operated on, and in the light of our experience today would not be subjected to surgery. All of these had drainage abscesses with secondary infection, tuberculosis of the lungs in a quiescent stage, and were not in good general condition.

In one case the graft was infected; the patient was not relieved and died about three years after operation of causes unknown. Two patients (2.7 per cent.) are not at all benefited by the operation, though still alive. These also were in advanced stages and probably should not have been submitted to surgery.

TUBERCULOSIS OF THE SPINE (JULY, 1912–JULY, 1916)

```
Cases observed.......................................... 274
Cases operated.......................................... 81
Cases reported.......................................... 73
Sex:
    Males.............................................. 51
    Females............................................ 30
Age:
    Average, 25; oldest patient, 53; youngest, 2.
Location of disease:
    Dorsal, 36; lumbar, 34; dorsolumbar, 11.
Cured.......................................... 42.4 per cent.
Relieved....................................... 45.2 per cent.
Not relieved................................... 2.7 per cent.
Operative deaths............................... 0
Average disability............................. 1½ years
Died later (two of these were cured of their spinal dis-
    ease)...................................... 7 (9.5 per cent.)
```

CONCLUSIONS

1. Neither the Hibbs nor the Albee type of operation for ankylosing the diseased area in tuberculosis of the spine is in any sense a radical operation for extirpation of the focus of disease.

2. Patients submitted to these procedures should be in good general condition. Paraplegia per se is not a contraindication.

3. Children are easily controlled on a gas-pipe frame and should be operated on only after careful consideration. The recumbent treatment should be carried out after operation until a cure is attained. In adults after operation and recumbency for at least four weeks a suitable brace should be provided to be worn until symptoms are entirely absent.

4. These procedures in themselves are not serious. A proper selection of patients will give a high percentage of cure and considerably shorten the period of treatment.

REFERENCES

1. Albee, F. H.: "Transplantation of a Portion of the Tibia into the Spine for Pott's Disease," Jour. Amer. Med. Assoc., 1911, lvii, 885–886.
2. Hibbs, R. A.: "An Operation for Progressive Spinal Deformities," New York Med. Jour., 1911, xciii, 1013–1016.

ELECTIVE LOCALIZATION OF BACTERIA IN DISEASES OF THE NERVOUS SYSTEM *

EDWARD C. ROSENOW

Many bacteria retain for a long time the peculiar properties which determine their characteristic localization. The importance of studying the infecting power of some in which these properties are less fixed has not been sufficiently considered.

Some years ago I showed that the common occurrence of endocarditis in animals following intravenous injection of a staphylococcus from endocarditis and numerous strains of Streptococcus viridans from chronic infectious endocarditis depended to a certain extent on clump formation, and that simultaneously with the disappearance of this property, both from artificial cultivation and animal passage, endocarditis failed to develop.[1]

The importance of making injections soon after isolation of the bacteria was emphasized at that time. In 1909 Lewis and the writer[2] reported the isolation of a diplococcus from the thrombus in the portal vein in primary portal thrombosis, which produced retrograde thrombosis in radicles of the portal vein in a rabbit following intravenous injection. The full significance of the results of the animal experiments, however, was not realized at the time.

During my studies on the transmutation of pneumococci and streptococci[3] in which relatively avirulent strains were made virulent by successive animal passages, and highly virulent strains less virulent by cultivation, marked changes in localization following intravenous injection in animals were noted. At certain lower grades of virulence, endocarditis, arthritis, cholecystitis, ulcer of the stomach, myositis and iritis, respectively, occurred, while when the virulence was high, hemorrhages and edema of the lung and bronchopneumonia commonly occurred.

The latter observation is in accord with the results of Wadsworth.[4] The results suggested the possibility that diseases of widely different symptomatology might be due to strains of bacteria of the same or closely related species, but having peculiar localizing or infecting powers. Since then systematic cultures in which there was afforded a gradient of oxygen pressure have been made from diseased tissues in a series of diseases.[5] Streptococci frequently very sensitive to oxygen have been isolated in many instances from the involved tissues, often to the exclusion of other bacteria in rheumatic fever, arthritis deformans, appendicitis, ulcer of the stomach, cholecystitis, and myositis, and a diphtheroid-like streptococcus from the erythematous node in erythema nodosum. The streptococci from rheumatic fever and erythema nodosum especially showed a preference for partial anaërobiasis. Intravenous injection soon after isolation of these strains and commonly those from the respective focus of infection often showed a most marked tendency to localize electively in the tissues in animals corresponding to those involved in the spontaneous disease.[6] The lesions were truly elective in many instances. They approximated in type those of the spontaneous disease. The elective property or peculiar trophic condition of the streptococci in the foci of infection was undoubtedly an important factor in producing the diseases studied. The suggestion that other diseases the etiology of which was still obscure might have a similar origin was at hand.

By the use of the same or similar technic, verification of the results in ulcer have been brought forward by Gerdine and Helmholz,[7] Hardt,[8] and Moody.[9] The results in iritis have been verified and extended by Irons, Brown and Nadler.[10]*

I wish here to summarize briefly the results of an experimental study of the possible etiologic relation of localized foci of infection, especially in and about the teeth and tonsils, to diseases of the nervous system. The technic used was similar to that previously described. Owing to the wealth of material at my disposal in the Mayo Clinic and the willing coöperation of the patients and the members of the staff, favorable cases were selected for investigation. Effort was made to obtain bacteria for cultures from the depth of the focus by expressing the infected material from tonsils with a laryngeal mirror, and

* The apparent inability of some to corroborate these and the results on the transmutation work appear explainable as due to differences in technic and differences in the character of strains studied.

ELECTIVE LOCALIZATION OF STREPTOCOCCI AND STAPHYLOCOCCI IN THE NERVOUS SYSTEM

Source of Bacteria	Strains	Animals Injected	Appendix	Stomach or Du-odenum (Hemorrhage)	Stomach or Du-odenum (Ulcer)	Gallbladder	Liver	Pancreas	Intestines	Joints	Endocardium	Pericardium	Myocardium	Muscles	Kidney	Lung	Skin	Teeth	Nerve-Trunks	Meninges	Spinal Cord	Brain	Dorsal Roots
Multiple sclerosis	3	31	0	6	3	10	3	3	0	13	3	3	6	29	23	3	0	0	0	23	53	13	0
Sporadic anterior poliomyelitis	1	36	0	17	0	3	6	0	3	8	0	6	3	14	31	0	3	0	19	25	78	14	0
Transverse myelitis	1	21	5	24	19	0	0	0	33	14	14	0	14	24	10	10	5	0	5	50	67	24	0
Neuralgia	4	18	0	6	0	6	6	0	0	11	22	0	6	33	6	33	28	0	28	22	0	0	83
Multiple neuritis	1	19	11	11	5	5	0	0	11	22	5	16	11	27	16	32	0	0	79	0	5	5	0
Myositis and dental neuritis	1	24	0	13	0	8	0	0	0	4	13	0	4	71	13	0	0	50	46	0	0	0	0
"Myalgia"	12	29	3	10	14	3	3	0	0	48	24	0	28	93	17	3	3	0	7	7	3	3	0
Average incidence of lesions exclusive of specific strains			3	12	6	5	3	0	7	12	12	5	7	27	17	15	6	0	12	13	4	8	0

by aspirating the infected pockets about teeth with a sterile pipet. In the former it commonly happened that abscesses were ruptured, even in tonsils which appeared quite normal on the surface. These were usually situated in the pole of the tonsils. Tonsillectomy and extraction of teeth were done when indicated.

The cultures for injection were usually incubated at 33° C. in tall columns of ascites-dextrose broth (affording a gradient of oxygen pressure), for from eighteen to twenty-four hours, centrifugalized in the containers in which they were grown, the supernatant broth saved for filtration and for injection of animals, and the sediment suspended in sodium chlorid solution, so that 1 c.c. represented the growth from 15 c.c. of the broth culture. Animals of different species were injected, often in series, with doses ranging generally from 1 to 3 c.c. of the suspension for rabbits and guinea-pigs, and from 0.25 to 1 c.c. per kilogram of weight for dogs and goats. In many experiments smaller doses of the broth culture without centrifugalization were injected. In some the bacteria from emulsions of the tonsils and suspensions of the material expressed from the tonsils were directly injected.

Part of the material obtained from the patient was plated out and incubated on human blood-agar, aërobically and anaërobically. Smears and inoculations on blood-agar plates were made as a routine of the broth cultures and suspensions at the time of injection. In most instances the bacteria from the primary culture in the broth were injected. These cultures often contained a mixture of bacteria, but usually showed a great preponderance of streptococci and in some instances pure cultures of streptococci. While it was the rule to inject the bacteria from the primary cultures in broth, injections were made in some instances of pure cultures from single colonies on blood-agar plates or from lesions and blood of animals. It is noteworthy how promptly the non-pathogenic or saprophytic bacteria disappear in animals.

The particular microörganism responsible for the lesions in animals when mixtures were injected was determined by demonstrating its presence in the lesions and its absence in normal tissues (and blood) by means of cultures and sections, and by again producing similar lesions on reinjection of the pure culture.

In the table is given a summary of the results obtained in animals. The figures indicate the percentage incidence of focal lesions in the various organs. In a few instances the figures only approximate the actual occurrence of lesions in various organs because they were not looked for

in all the animals injected, the pulps of only four to six teeth and approximately three-fourths of the spinal roots being examined as a routine for lesions. Lesions in the liver, spleen, thyroid, lymph-glands, tonsils, tongue, parotid, eyes, and reproductive organs occurred so rarely that they are not included in the table. In the last line is given the percentage incidence of lesions in various organs exclusive of the specific strains. These figures serve as a basis for comparison. They correspond in a general way to those given in my previous table.[6] The incidence of arthritis, however, is less, while the incidence of myositis is greater. The latter is due to the frequent injection of slightly hemolyzing streptococci which commonly localize in muscles.

Lesions of the spinal cord, usually patchy in character, were observed in 58 per cent. of 31 animals injected with the bacteria from the tonsils or infected teeth in three cases of multiple sclerosis. In one of these the lesions appeared to be due to a staphylococcus; in the other two, to a green-producing streptococcus. Markedly increased reflexes, ataxia, and paraplegia were noted during life in some of the animals. None became paralyzed. The duration of symptoms in the patients ranged from three to eight years. In two additional cases little evidence of local infection was found and the cultures failed to produce lesions in the spinal cord.

Lesions of the spinal cord, consisting of numerous hemorrhages, especially in the anterior horns in the cervical region, were noted in 78 per cent. of 36 animals injected with the staphylococcus from the tonsil in a typical case of sporadic anterior poliomyelitis. Many of these developed partial or complete paralysis, more marked in the anterior extremities, both after intravenous and intracerebral injection of pure cultures and of emulsions of diseased cords. Several dogs showed marked improvement in motive power, and some obtained a complete restoration of movement. The lesions in the cord are quite different from those in epidemic anterior poliomyelitis.

Lesions of the meninges and spinal cord occurred in 50 per cent. and 66 per cent. of 21 animals injected with the bacteria as isolated from the pyorrheal pockets and tonsils in a case of transverse myelitis with paralysis of the lower extremities. Partial or complete paralysis, which began in the hind extremities, developed in many of these animals. The lesions of the cord consisted chiefly of hemorrhages both in the gray and white matter and of leukocytic infiltration in the meninges and surrounding the blood-vessels.

The occurrence of the two types of paralysis, following injection of the bacteria from these two cases, was a striking picture. It was difficult, and in some instances impossible, to demonstrate bacteria in the areas of hemorrhage showing little or no leukocytic infiltration in the substance of the cord. They appeared to be infarctions from partial or complete thrombosis of the small blood-vessels remote from the area of hemorrhage. This was true alike following injections in multiple sclerosis, anterior poliomyelitis, and transverse myelitis. The bacteria were found in large numbers in the areas of infiltration in the meninges and surrounding blood-vessels in transverse myelitis. These findings are in accord with the fact that bacteria are rarely findable in acute myelitis in man, and hence the lesions are thought to be toxic in origin or due to filterable viruses.

Lesions in or about one or more of the posterior roots occurred in 83 per cent. of 18 animals following injection of streptococci from cases of brachial, intercostal, and postherpetic neuralgia. The occurrence of neuritis in 28 per cent. of these animals is noteworthy. This and the high incidence of lesions in the skin, 28 per cent. (chiefly herpes), occurred in animals injected with relatively large doses. As far as can be determined this is the first experimental demonstration of the probable nature of this form of neuralgia.

Lesions of the peripheral nerves occurred in 79 per cent. of the 19 animals injected with the pneumococcus obtained on two occasions from multiple neuritis. In one rabbit typical wrist-drop developed. The animals seemed to be in pain. The lesions consisted of localized hemorrhages, edema, and leukocytic infiltration, in which often many diplococci were found. The localization of the slightly hemolyzing streptococcus isolated from the dead pulp of a tooth and excised muscle from the neck in a case of myositis and dental neuritis was unique: 71 per cent. of the 24 animals injected showed myositis, 50 per cent. dental pulpitis, and 46 per cent. neuritis, chiefly of the dental nerves.

Lesions in or about the joints occurred in 48 per cent. of the 29 animals injected, in the myocardium in 28 per cent., and in the muscles in 93 per cent., following injection of the cultures (all containing slightly hemolyzing streptococci) from the 12 cases of "myalgia" (cases of fibrositis or mild myositis, with or without periarthritis). These were included in this table to show the contrast in distribution of lesions and because in some cases it appeared that some of the pain was due to mild neuritis.

It must not be supposed that the lesions observed were slight or temporary, that they were always the result of the injection of large doses (even the small amount of exudate expressed from tonsils when directly injected was sufficient to produce the lesions in some instances), or that they were usually a part of a generalized fatal infection (62 per cent. of the animals recovered and were chloroformed for examination). Localizations strikingly like those in the patients were obtained in many animals of different species with the bacteria as isolated, but not with the same strains after cultivation for a time or after a number of successive animal passages. In those strains in which the elective property was marked the characteristic localization occurred in nearly all the animals injected intravenously and in a high percentage of those injected intraperitoneally. Numerous strains from other sources and the filtrate of the broth cultures of the strains as isolated have failed to cause similar lesions. These and other facts preclude the possibility that the lesions in the animals were from spontaneous or accidental causes.

The conclusion seems warranted that the lesions in the patients studied were due to hematogenous infection from a focal source by the bacteria isolated. The improvement in symptoms following removal of foci of infection which were proved to harbor bacteria with peculiar localizing powers in multiple sclerosis, transverse myelitis, several cases of persistent neuralgia (although not in others), and in the case of dental neuritis and myositis speaks in favor of this view. The results emphasize the importance of thorough search for foci of infection and, if possible, their removal in diseases of the nervous system. In the light of these results and much clinical evidence, as emphasized especially by Billings, a chronic focus of infection which cannot heal for mechanical reasons, often teeming with bacteria, must be considered as a test-tube with a permeable wall embedded in the tissues, which, as I have already pointed out,[6] affords not only abundant opportunity for the entrance of bacteria and their products, but also. the conditions favoring the acquisition of various infective powers by the bacteria. The demonstrated presence over a long period of time in foci of infection (particularly in chronic diseases) of bacteria with the same elective localizing powers suggests that the tendency to recurrences of a certain type of disease in the same patient and even hereditary tendencies may be due in part to the peculiar environment furnished by the individual which may favor the acquisition and maintenance by the bacteria of a particular infecting power.

Too much benefit should not be expected from the removal of evident foci of infection, because a similar condition may be present in inaccessible foci and in others too small to be detected. Moreover, recovery may be made difficult by local tissue sensitivity or peculiar mechanical conditions, and living bacteria in a metastatic lesion may continue the process independently of the focal source. In the case of dental neuritis and myositis the focus was found in the pulp of a dead molar tooth, no demonstrable lesions being found in the jaw. The removal of the tooth, while helpful, was not followed by the prompt disappearance of the symptoms. Streptococci demonstrated in sections of the excised muscle from the neck were proved alive ten days after a typical recurrent attack of spasm and pain.*

REFERENCES

1. Rosenow, E. C.: "Immunological and Experimental Studies on Pneumococcus and Staphylococcus Endocarditis," Jour. Infect. Dis., 1909, vi, 245-281; "Immunological Studies in Chronic Pneumococcus Endocarditis," Jour. Infect. Dis., 1910, vii, 429-456; "Further Immunological Studies in Chronic Pneumococcus Endocarditis," New York State Jour. Med., 1912, xii, 441-445; "Experimental Infectious Endocarditis," Jour. Infect. Dis., 1912, xi, 210-224.
2. Lewis, D. D., and Rosenow, E. C.: "Primary Portal Thrombosis," Arch. Int. Med., 1909, iii, 232-248.
3. Rosenow, E. C.: "Transmutations Within the Streptococcus-Pneumococcus Group," Jour. Infect. Dis., 1914, xiv, 1-32.
4. Wadsworth, A. B.: "Studies on Pneumococcus Infection in Animals," Trans. Assoc. Amer. Phys., 1912, xxvii, 72-82; "Pneumonia; a Bedside and Laboratory Study," Amer. Jour. Obst., 1909, lix, 1080-1084.
5. Rosenow, E. C.: "The Newer Bacteriology of Various Infections as Determined by Special Methods," Jour. Amer. Med. Assoc., 1914, lxiii, 903-907.
6. Rosenow, E. C.: "Elective Localization of Streptococci," Jour. Amer. Med. Assoc., 1915, lxv, 1687-1691.
7. Gerdine, L., and Helmholz, H. F.: "Duodenal Ulcer in Infancy an Infectious Disease," Amer. Jour. Dis. Child., 1915, x, 397.
8. Hardt, L. L. J.: "The Secretion of Gastric Juice in Cases of Gastric and Duodenal Ulcers," Amer. Jour. Physiol., 1916, xl, 314-331.
9. Moody: Personal communication to the author.
10. Irons, E. E., Brown, E. V. L., and Nadler, W. H.: "The Localization of Streptococci in the Eye. A Study of Experimental Iridocyclitis in Rabbits," Jour. Infect. Dis., 1916, xviii, 315-334.

* The details of the clinical histories and the experiments, a review of the literature, and a more detailed discussion of the significance of the findings, are reserved for separate papers.

EPIDEMIC ANTERIOR POLIOMYELITIS

STUDY I.—THE ETIOLOGY OF EPIDEMIC POLIOMYELITIS PRELIMINARY NOTE*

EDWARD C. ROSENOW, EDWARD B. TOWNE, AND GEORGE W. WHEELER

After Landsteiner and Levaditi[1] and Flexner and Lewis[2] demonstrated independently that the causative agent of epidemic poliomyelitis could be passed through a bacterial filter, the disease was classed with those caused by a filterable, ultramicroscopic virus. The bacteria of ordinary size were no longer considered of etiologic importance, and when obtained were discarded as postmortem invaders or accidental contaminations. Wickman,[3] after reviewing the earlier experiments with streptococci, says: "The time has fully arrived when such investigations should be discarded from the literature of the disease."

In 1913 Flexner and Noguchi[4] cultivated and demonstrated microscopically a small filterable microörganism with which they produced poliomyelitis in monkeys. They note that "the cultural conditions are those that apply more particularly to the bacteria," but do not attempt definitely to classify the microörganism.

Rosenow[5] has shown by the use of special methods that the specific localizing power of bacteria is an important factor in the etiology of various diseases, including diseases of the nervous system. We felt, therefore, that a reinvestigation of the bacteriology of poliomyelitis by the newer methods was desirable. Accordingly, we have made a bacteriologic study of throats, tonsils, blood, spinal fluid, the central nervous system and other tissues in cases of acute poliomyelitis in the present epidemic, both in Rochester, Minn., and in New York City, with particular reference to the infecting power of the bacteria isolated. The methods employed were similar to those used by Rosenow, and the methods used by Flexner and Noguchi in their studies of poliomyelitis.

A peculiar polymorphous streptococcus has been isolated, often in large numbers, from the throat, from the material expressed from tonsils, and from abscesses in tonsils* (Fig. 353) of a large series of cases of epidemic poliomyelitis. It has been obtained from the ventricular fluid after death, and from blood during life in one instance, but not from the spinal fluid. By emulsifying in a sterile air chamber a rather large amount of brain and cord obtained under sterile precautions, and inoculating ascites-dextrose broth, ascites-dextrose agar, and ascites fluid containing sterile tissue with varying amounts of the emulsion, we have succeeded in isolating this peculiar streptococcus from brain and cord in each of twelve cases of poliomyelitis in New York City which came to necropsy, and also from the intervertebral ganglia and lymph-nodes in some of these cases. Mathers[6] has already reported similar results from the brain and cord. The microörganism has also been recovered in four instances from recently glycerinated pieces of brain and cord.

The microörganism which we have isolated in cases of human poliomyelitis produces on aërobic blood-agar plates fine, dry, non-adherent, slightly green colonies at times showing in forty-eight hours a narrow, hazy zone of hemolysis. On this medium, as well as in ascites-dextrose agar, the organisms are quite uniform in size and resemble pneumococci, but are usually smaller and free from demonstrable capsule. In tall tubes of ascites-dextrose broth

Fig. 353.—Cross-section of Kaiserling specimen of left tonsil removed four hours postmortem in Case 758; acute poliomyelitis in child aged fifteen months (× 2½). Part of the material in the abscess cavity, which lies against the capsule of tonsil, fell out during hardening.

with or without sterile tissue there is usually an early diffuse turbidity, or there may be a flocculent growth which collects along the side of the tube and gradually settles to the bottom. Early smears show short chains of diplococci resembling pneumococci, a smaller number of medium-sized cocci in pairs, and occasionally very small coccus forms. After the first week the number of small forms is relatively greater, and they have largely become Gram-negative. After about three weeks large clubbed involution forms appear. In ascites plain broth with or without sterile tissue, growth is slower, being noted usually after about thirty-six hours. It tends to

* The importance of the constant finding of such abscesses in tonsils at necropsy in cases of poliomyelitis was emphasized in a discussion by Rosenow of Dr. Robert W. Lovett's paper, "The Management of Poliomyelitis," before the New York Academy of Medicine, October 5, 1916.

appear near the bottom of the tube and extends upward as a moderate turbidity. The organism has the same morphologic characteristics, but is about two-thirds the size of that grown in dextrose broth. Old cultures show clumps of very small coccus forms. In ascites fluid containing sterile tissue the growth appears as a slight haziness near the bottom of the tube on the fourth or fifth day when cultures are made of human or animal brain and cord. Transplants from other mediums grow out in one or two days, and show more marked early turbidity. In a very few instances the early smears have shown the tiny globoid bodies described by Flexner and Noguchi in apparently pure culture, but usually there have also been a certain number of medium-sized diplococci in short chains, which Flexner and Noguchi and others have considered contaminations. These larger forms tend to grow smaller, so that frequently at the end of twelve or fourteen days nothing but the tiny globoid bodies, single, in pairs, chains and clumps, could be found in the same tubes. These appear to be identical with those described by Flexner and Noguchi. After about three weeks the organisms become both larger and smaller; the small forms get beyond the limit of visibility, and nothing but rather large oval cocci staining a pinkish tint with the Giemsa stain are seen.

Transplants from one to another of these three liquid mediums disclose a marked tendency of the microörganism to change to the form characteristic of the medium in which it is planted. Thus, an apparently pure culture of the very small globoid bodies in ascites tissue fluid when transferred to ascites-dextrose tissue broth grows out rapidly, often in twenty-four hours, into the characteristic polymorphous streptococcus. Similarly a transplant from broth to ascites fluid tends to grow slowly smaller.

Cultures of Berkefeld N filtrates of emulsions of brain and cord of rabbits dead from paralysis following intravenous injection with suspensions of broth cultures showing only the large forms have repeatedly grown out in this characteristic form in each of these three culture-mediums. Cultures showing the small forms have been filtered, and cultures of the filtrate have grown, but no growth has been obtained from filtrates of cultures of the same strains showing only large forms. The same emulsions filtered through dense porcelain candles have, with one exception, always been sterile.

In all the liquid mediums during the early days of growth chains are often found in which there are single members of all sizes and shapes—

large diplococci, large coccus forms, small diplococci, and small coccus forms. This has occurred in strains which have been fished successively several times from single colonies of shake and plate cultures, and in those from filtrates (Fig. 354).

The fermentative reactions of subcultures of a number of these strains have been tested. Two-thirds of them fermented inulin; the remainder did not.

Paralysis with lesions in the central nervous system has been produced in guinea-pigs, rabbits, dogs, cats, and monkeys by intravenous or intracerebral injection with this peculiar streptococcus from practically all of 52 cases of acute polio-myelitis. It has been produced by injecting the emulsions of pus expressed from the tonsils, emulsions of extirpated tonsils, and emulsions of the brain. It has followed injection of the primary mixed culture containing chiefly this peculiar streptococcus, and by injection of the pure cultures from throats, from the material expressed from tonsils, and from the abscesses in tonsils removed from living patients and necropsy cases. It has been produced consistently also with the pure cultures obtained from the brain and cord. While on aërobic cultivation and in dextrose-containing mediums the organism soon

Fig. 354.—Photomicrograph of forty-eight-hour culture in ascites-dextrose tissue broth of Berkefeld N filtrate of emulsion of brain of Rabbit 1017, injected intravenously with pure culture of the streptococcus from poliomyelitis after two rabbit passages. Note the marked variation in size and shape of the organism, the chain of large diplococci and micrococci with a small diplococcus on one end, chains of medium and small diplococci and those of extremely small diplococci and the medium-sized single coccus forms. Gram stain (× 1000).

loses the power of causing paralysis, paralysis has been produced with strains in the third culture generation from successive single colonies.

Young animals were more susceptible, but the older ones were not always immune. While those which received large doses of culture often showed paralysis within thirty-six hours, the incubation period was usually from three to five days. The early paralyses were usually accompanied by evidences of pain in the affected extremity, and the animals so affected were apt to die within twenty-four hours of the onset, as the process extended rapidly and caused respiratory failure. The onset of later paralyses, especially in rabbits, was sometimes preceded

by a fine tremor or even definite twitching of the muscles which later became flaccid. These animals appeared generally well, and took food normally. In most cases the paralyses spread and death occurred within two or three days. A number of animals, however, showed slow but definite improvement and did not die. One guinea-pig had a ptosis, and one monkey a seventh nerve paralysis, as initial symptoms. In some the reaction began with evidence of meningeal irritation which went on to general spasticity, convulsions, and rapid death.

At necropsy the paralyzed animals showed congestion of the vessels of the meninges, and hemorrhagic edema surrounding the dura of the cord, especially anteriorly and extending along the nerve-roots and ganglia. A majority had dilatation and fine hemorrhages in the gray matter of the cord and brain. The lymph-glands commonly showed hyperemia and at times hemorrhage and edema. Animals which had ataxia and tremor usually showed areas of hemorrhagic infiltration of the cerebellum. There was a noteworthy freedom of lesions in other organs. Microscopic sections have not yet been examined in sufficient numbers to warrant a definite report, but those examined (from rabbits, guinea-pigs, and monkeys) showed small hemorrhages, degeneration of nerve-cells, some round-cell infiltration, and neurophagocytosis.

The organism has been isolated in pure culture and often in large numbers from the nervous tissue in numerous animals injected with cultures when blood and other tissues were sterile or contained the organism in smaller numbers. It has been demonstrated microscopically in, and adjacent to, the lesions in the brain and cord. In animals in which paralysis occurred early and which died soon after injections of large doses, the large forms only have thus far been found, while in those which died after a long period of incubation, both large and small forms have been demonstrated.

We have isolated the same organism from brain and cord of paralyzed monkeys injected intracerebrally with fresh emulsions of brain and cord from human poliomyelitis (fresh human virus), with glycerinated human virus and glycerinated monkey virus.*

ILLUSTRATIVE EXPERIMENTS

CASE 686.—S. A., boy aged five years, complained of stiff neck July 18. July 20 he had a temperature of 102° F. When seen with Dr. Sheldon in the Mayo Clinic, July 21, there was weakness of the

* Kindly sent us by Dr. G. W. McCoy, of the U. S. Public Health Service, Washington, D. C.

left shoulder and arm, and flaccid paralysis of the left deltoid, triceps, and scapular muscles. The left grip was weaker than the right; the fingers moved slowly, and there was evidence of extensor weakness. No reflexes could be obtained in the left arm.

From the left tonsil there was expressed a soft greenish plug, about 1.5 by 2.5 mm., and from both tonsils a rather large amount of liquid pus was obtained.

The material expressed from the tonsils was emulsified in 2 c.c. of salt solution, and cultures and animal injections were made. One series of rabbits and guinea-pigs was injected immediately with the emulsion of the tonsil pus, and another series, July 22, with the cultures.

Eighteen-hour cultures of the tonsil pus gave the following results:

1. Blood-agar plate showed enormous numbers of very fine, dry, green-producing streptococcus colonies, some of which were surrounded by a narrow zone of hazy hemolysis and a few colonies of staphylococcus and Micrococcus catarrhalis.

2. Ascites-dextrose broth (tubes and bottles) showed apparently pure cultures of streptococci in short and medium long chains and in pairs. Some of the diplococci were large and lanceolate in shape, resembling pneumococci, and others were small and more coccus-like. Both large and small forms were found in the same chain.

In all, injections were made into 13 animals—7 rabbits, 5 guinea-pigs, and 1 dog. Of these, the dog and all but one of each of the rabbits and guinea-pigs showed either evidence of paralysis during life or lesions of the brain and cord after death. The following three protocols illustrate the results obtained:

RABBIT 930.—Weight, 690 gm. July 21, an injection of 0.5 c.c. of sodium chlorid emulsion of tonsil pus (Case 686) the organisms of which appeared on blood-agar plates as fine, green-producing streptococci, slightly hemolytic streptococci, staphylococci, and Micrococcus catarrhalis, was made into the cerebrum. The animal was found dead eighteen hours later. Necropsy revealed lesions of skeletal and heart muscles but no external abnormality of brain or cord. Cultures of the blood were sterile. Ascites-dextrose broth and blood-agar plate cultures of the spinal cord showed pure cultures of streptococci, appearing as fine, dry, green colonies on the plate. In sections of the brain and cord after hardening seven small hemorrhages were found in the gray matter of the cord and two larger hemorrhages in the anterior portion of the medulla. Microscopically, these areas showed hemorrhage, slight round-cell infiltration, and diplococci and streptococci in the vicinity of the hemorrhagic areas.

RABBIT 936.—Weight, 1040 gm. Injected intravenously, July 24, with a growth from 30 c.c. of ascites-dextrose broth suspended in 2 c.c. sodium chlorid solution of the spinal cord of Rabbit 930. Blood-agar plates of the culture injected showed fine, dry, green-producing strepto-

coccus colonies in pure culture. The rabbit was found dead the next morning. Necropsy showed no focal lesions. Ascites-dextrose broth culture of blood gave an apparently pure culture of streptococci in pairs and short chains. A blood-agar plate of blood showed a pure culture of very small, dry, green-producing streptococcus colonies, a few of which were surrounded by a narrow, hazy zone of hemolysis.

RABBIT 939.—Weight, 1160 gm. Injected intravenously July 26 with 5 c.c. of an ascites-dextrose broth culture of the blood of Rabbit 936. The animal seemed perfectly well up to August 11, sixteen days after the injection, when at 11
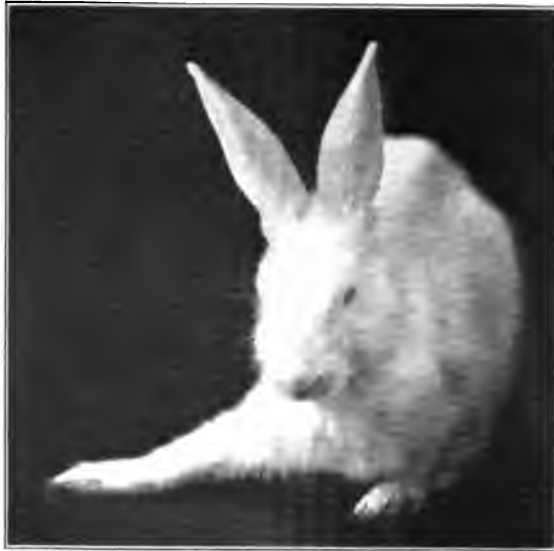
Fig. 355.—Rabbit 939, showing flaccid paralysis of right front leg, August 11, 1916.

Fig. 356.—Rabbit 939. sections of Kaiserling specimen of cord (× 2). From above downward Sections 1, 2, 3, 4, and 5 are cervical cord; Sections 6 and 7 dorsal cord; Section 8 lumbar cord. Note hemorrhages in gray matter, chiefly in anterior horns.

A. M. it showed flaccid paralysis of the right front leg, which lay stretched out and could not be brought under the body (Fig. 355). Otherwise he seemed well, and took food normally. At 3 P. M. the left front leg was also weak, and he was unable to lift the thorax from the floor. At 4 P. M. respiration became shallow, irregular, and labored; there was evidence of meningeal and cerebral involvement (retraction of head and convulsions). Death occurred at 5 P. M. Necropsy showed no gross lesions. August 12 the spinal cord and fluid incubated over night showed diplococci, short chains, and clumps of

Fig. 357.—Photomicrograph of cross-section of cerebrum of Rabbit 939, showing diffuse infiltration of small round-cells. No red cells present.
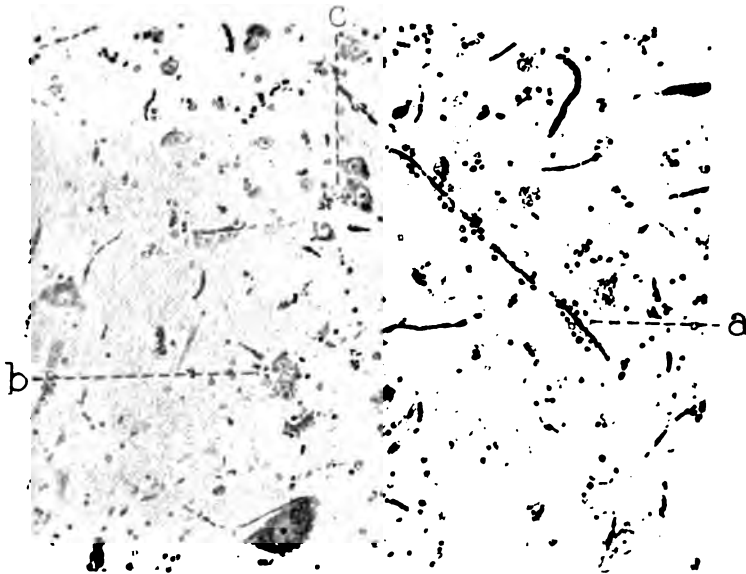
Fig. 358.—Photomicrograph of cross-section of the upper part of anterior horn of cervical cord of Rabbit 939. Note the hyperemia and hemorrhages (a), the adventitial small round-cell infiltration, (b) the degeneration of ganglion-cells, (c) satellitosis and neurophagocytosis.

'16—52

streptococci. The individual organisms in chains showed marked difference in size, varying from approximately one-fourth that of a pneumococcus to the full size of a pneumococcus. Cross-sections of the cord after fixation in Kaiserling I for twenty-four hours showed diffuse hyperemia of the gray matter throughout, and areas of hemorrhage in the gray matter which were most marked in the cervical region (Fig. 356). Microscopic sections of all portions of the cord showed many small and medium-sized areas of hemorrhage in the gray matter, especially in the anterior horns. Moderate round-cell infiltration was noted throughout the gray matter (Fig. 357). The ganglion-cells, particularly of the anterior horns in the cervical region, showed marked degeneration and neurophagocytosis (Fig. 358). In the intervertebral ganglia there were degeneration and phagocytosis of the ganglion-cells and moderate lymphocytic infiltration. Gram stains of sections of the cord showed rather small Gram-positive diplococci, single and in short chains. In several areas of hemorrhage showing deposit of blood-pigment there were found large numbers of cocci, some in pairs and chains, showing marked variation in size (Fig. 359).
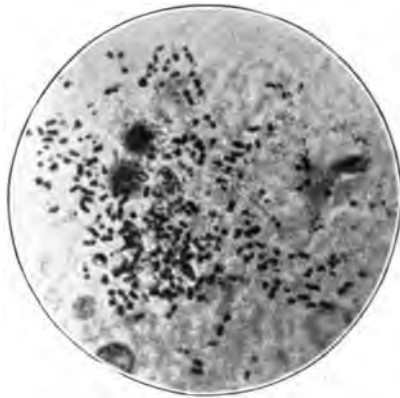
Fig. 359.—Photomicrograph of streptococcic forms in area of hemorrhage in the posterior horn of cervical cord of Rabbit 939. Note the marked variation in size of the organisms, large and small diplococci scattered throughout the field, and exceedingly small forms in the short chains to the left of the center. The dark, irregular areas to the left are deposits of blood-pigment. Gram-Weigert (× 1000).

CASE 714.—Monkey 12 (Macacus rhesus) was injected intravenously, September 9, with suspensions in salt solution of the growth from 30 c.c. of ascites-dextrose and 30 c.c. of plain broth, mixed, obtained from the brain of Rabbit 1017 in pure culture. This organism formed characteristic fine, dry, green colonies on blood-agar plate and appeared as an ordinary-sized streptococcus in broth. The strain came from the emulsions of brain in a case of poliomyelitis in which the necropsy was made August 24, and had passed in pure culture of large forms through three rabbits in succession. Each rabbit had shown marked flaccid paralysis after from three to seven days with gross and microscopic lesions quite similar to those described above for Rabbit 939.

September 11, the left arm was weak; slight wrist-drop and poor grip. The animal took food normally and seemed well.

September 12, condition of arm was stationary, or perhaps improved a little. The animal was injected intravenously with the growth from 30 c.c. of the same culture, which in the meantime had been in the icebox, and showed the same growth in subculture on plate and in broth.

September 14, both arms were weak. The animal was irritable and excited.

September 15, the animal was quiet and inclined to lie down; it got on its haunches with great difficulty.

September 16, complete wrist-drop was shown on left, flaccid paralysis of left triceps and deltoid, weakness of back muscles, and coarse tremor of right triceps and extensors of thighs. The animal ate well if food was put where he could reach it with his head. This condition went on to complete flaccid paralysis of all muscles of extremities and body; respiration became irregular, labored, and entirely diaphragmatic.
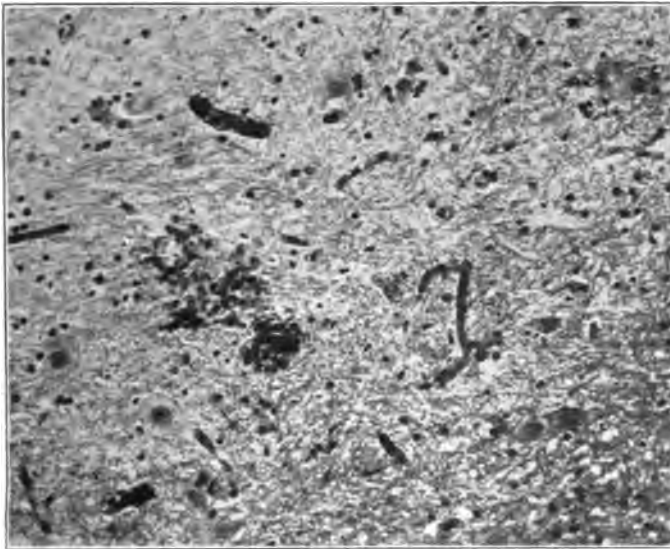
Fig. 360.—Photomicrograph of cross-section of anterior horn of cervical cord of Monkey 12. Note the marked dilatation of vessels, the hemorrhage, the degeneration of ganglion-cells, and round-cell infiltration with neuronophagia. Hematoxylin and eosin (× 140).

Marked cyanosis. At 7.30 P. M. the animal was almost dead; he was chloroformed, and examined at necropsy at once.

Cross-sections of the cord showed hyperemia of the gray matter with areas of hemorrhagic infiltration, more marked in anterior horns and about the central canal. There were no other gross lesions. Cultures of the brain and cord gave the usual polymorphous streptococcus in pure culture in almost every tube. Microscopic sections of the cord (Fig. 360) showed numerous hemorrhages in the gray matter, with degeneration of the ganglion-cells of the anterior horns. There was moderate infiltration with lymphocytes and neuronophagia. Diplococci were demonstrated in the tissues.

SUMMARY

We have isolated a peculiar streptococcus from throats, tonsils, abscesses in tonsils, and from the central nervous system in cases of poliomyelitis.   Paralysis has been produced in animals of various species by intravenous and intracerebral injection of cultures of this organism, and lesions of the gray matter of their nervous system have been demonstrated.   From the nervous system of these animals the streptococcus has been isolated in pure culture, while their other tissues were sterile; it is remarkably polymorphous, and appears to grow large or small according to the medium in which it is grown, even after passage through a Berkefeld filter.

Using the organism in its large form, paralysis has been consistently produced in animals known to be insusceptible to inoculation with material from epidemic poliomyelitis as heretofore practised.   After paralysis had been produced in a series of three rabbits, the strain caused characteristic paralysis and lesions of poliomyelitis in monkeys.

The exact relation of our results to the facts already established as to the etiology of poliomyelitis cannot yet be definitely stated.   It appears to us that the small, filterable organism which has been generally accepted as the cause of poliomyelitis may be the form which this streptococcus tends to take under anaërobic conditions in the central nervous system and in suitable culture-mediums, while the larger and more typically streptococcic forms, which investigators have considered contaminations, may be the identical organism grown larger under suitable conditions.

STUDY II. OBSERVATIONS ON IMMUNITY OF MONKEYS TO EXPERIMENTAL POLIOMYELITIS[*]

It is a generally accepted fact that a monkey, after recovery from an attack of experimental poliomyelitis, is immune to subsequent injection with virulent virus.   It is a debated question whether an inoculation which does not cause paralysis confers immunity.   Römer believes that immunity follows unsuccessful intracerebral injection in some cases. But there are in the literature many instances in which experimental

poliomyelitis has been produced in monkeys that had shown no evidence of infection from a previous inoculation.

We wish to record an experiment which appears to indicate that immunity was conferred upon three monkeys by inoculations which were not followed by obvious evidence of infection. One of the apparently immune animals had previously received an intracerebral injection of a culture of pleomorphic streptococci; the second had received emulsion of central nervous system of animals paralyzed by cultures of streptococci; and the third had received virus in the usual way.

Material Used for Test Inoculation.—A virus which had been passed successively through four monkeys was employed. A 5 per cent. emulsion in normal salt solution of the brain and cord of the fourth animal (Monkey 26) was made immediately after necropsy on November 3. This was ground thoroughly with sterile quartz sand and shaken for twenty minutes. Eight rhesus monkeys were injected in the left frontal lobe with this emulsion. Two of these were controls; five had received previous inoculations with virus, filtrate of virus, or culture; and the eighth had received a mixture of the test virus and blood-serum from monkeys suspected of being immune. Seven of the monkeys which were of approximately the same weight were given 1 c.c. of the test virus; and the eighth, which was a large, old animal, was given 3 c.c.

The accompanying table briefly records the results of this experiment. For details of the source of material used in the previous injections reference should be made to the protocols.

PROTOCOLS

EXPERIMENT 1.—*Control.*—Monkey 33, Macacus rhesus, 2.6 kilos.

November 3, 1916: Etherized. 1 c.c. of Virus 751[5] injected into left frontal lobe.

November 10 (seventh day): Tremor of arms and legs, rapidly followed by flaccid paralysis of left arm and marked weakness of muscles of the right arm, back, and legs.

November 11: Prostrate. Killed with ether. Cyst size of pea, filled with clear fluid, was found at point of inoculation. Microscopic section of brain and cord showed marked typical lesions of experimental poliomyelitis.

EXPERIMENT 2.—*Control.*—Monkey 34, M. rhesus, 7.3 kilos.

November 3: 3 c.c. of Virus 751[5] injected into the left frontal lobe. Immediately after injection there was spastic weakness of the right arm.

November 7: Several convulsions. Right arm remained almost

RESULTS OF TEST INJECTIONS OF A VIRULENT VIRUS

	1 Monkey 33, M. Rhesus, 2.6 Kilos (Control)	2 Monkey 34, M. Rhesus, 7.3 Kilos (Control)	3 Monkey 37, M. Rhesus, 2.8 Kilos	4 Monkey 21, M. Rhesus, 2.3 Kilos	5 Monkey 24, M. Rhesus, 2.3 Kilos	6 Monkey 17, M. Rhesus, 2.5 Kilos	7 Monkey 14, M. Rhesus, 2.1 Kilos	8 Monkey 19, M. Rhesus, 2.8 Kilos
Previous injection:				September 16 and 21, growth from 60 c.c. and 20 c.c. of Broth-culture 756 (Monkey 18, teeth) intravenously (not poliomyelitis).	October 5, 1.5 c.c. Berkefeld filtrate Virus 787² (Monkey 16) intracerebrally (not poliomyelitis).	September 13, 1.5 c.c. porcelain filtrate Virus 787 intracerebrally. September 19, 0.75 c.c. Virus 729 intracerebrally.	September 13 and 20 intracerebral injection filtrate and Virus 714³ (Monkeys 10 and 12, paralyzed with cultures).	September 16, 1.5 c.c. Cultures 707.2 intracerebrally.
Result of previous injection:				September 17, well thereafter.	Remained well.	Remained well.	September 18, right arm awkward. Well thereafter.	September 16-18 sick. Well thereafter.
Test injection Virus 751⁵ (Monkey 26):	November 3, 1 c.c. intracerebrally.	November 3, 3 c.c. intracerebrally.	November 4, 1 c.c. virus + 1 c.c. serum Monkeys 19 and 21 (incubated 2.5 hours) intracerebrally.	November 3, 1 c.c. intracerebrally.	November 3, 1 c.c. intracerebrally.	November 3, 1 c.c. intracerebrally.	November 3, 1 c.c. intracerebrally.	November 3, 1 c.c. intracerebrally.
Result:	Paralysis seventh day. Killed with ether eighth day. Typical lesions.	Tremor tenth day. Paralysis thirteenth day. Killed with ether fourteenth day. Typical lesions.	Excitement and tremor fifteenth day. Paralysis seventeenth day. Killed with ether seventeenth day. Typical lesions.	Tremor sixteenth day. Paralysis seventeenth day. Prostrate twenty-third day. Improved thirty-second day. Weak legs with contractures forty-fifth day.	Ataxia, squint, and paresis seventh day. Paralysis fourteenth day. Improved twenty-third day. Weak arm and squint forty-fifth day.	No symptoms. Well on forty-fifth day.	No symptoms. Well on forty-fifth day.	No symptoms. Well on forty-fifth day.

useless and there was slight weakness of right face and leg. Acted as if sick and ate little.

November 10: Better; took food well and was active; the right arm still weak.

November 13 (tenth day): Irritable. Coarse tremor of left arm.

November 15: General tremor. Legs weak; could scarcely walk. Handling legs appeared to cause pain. Knee-jerks exaggerated.

November 16: Legs flaccid; reflexes abolished. Left arm tremulous and weak; back muscles weak. Difficulty in swallowing. Killed with ether. A cyst about the size of an almond, filled with clear, deep yellow fluid (old blood), was found at point of injection. Microscopic sections of brain and cord showed typical lesions of experimental poliomyelitis.

EXPERIMENT 3.—*Attempt to destroy activity of virus by mixing with serum of monkeys thought to be immune.* Monkey 37, M. rhesus, 2.8 kilos.

November 3: Virus-serum mixture made as follows: Blood was removed from the internal saphenous vein of Monkeys 19 and 21 (*q. v.*) previous to their inoculation with the test virus. The sera were mixed so that 1 c.c. contained approximately 3 parts from Monkey 19 and 7 parts from Monkey 21, and 1 c.c. of the serum mixture was added to 1 c.c. of the test virus. The mixture was filtered through paper, kept at a temperature of 35° C. for 2.5 hours, and then in the ice-box for fifteen hours.

November 4: Etherized, and 2 c.c. of virus-serum mixture (containing 1 c.c. of Virus 751[5]) injected into left frontal lobe.

November 19 (fifteenth day): Very excitable. Head inclined to the right; constant coarse tremor of right neck muscles.

November 20: Tremor has extended to muscles of right arm. Knee-jerks brisk.

November 21: Flaccid paralysis of legs, back, and right arm. Left arm weak and tremulous. Killed with ether. Small cyst containing clear fluid at the point of inoculation. Microscopic sections showed characteristic lesions of experimental poliomyelitis.

EXPERIMENT 4.—*A monkey previously injected intravenously with culture from pus about the teeth of a monkey which did not have pathologic lesions of poliomyelitis was not immune to test virus.* Monkey 21, M. rhesus, 2.5 kilos.

Previous inoculation, September 16, 1916. Injected intravenously with 4 c.c. of a suspension in normal salt solution of the centrifugalized growth from 60 c.c. of ascites-dextrose broth culture of pus around the teeth of Monkey 18, Case 756. This organism appeared in smears from broth as a somewhat elongated diplococcus, occasionally in short chains; and on blood-agar plate as small, dry, green-producing colonies. (Monkey 18 was a domesticated monkey, with marked pyorrhoea alveolaris; he became spontaneously paralyzed in the animal room. When muscle

power began to come back, he was killed with ether.   Microscopic sections did not show lesions of poliomyelitis.)

September 17: Sick and irritable.

September 21: Appeared well.   Etherized.   Injected into frontal lobe 1.3 c.c. of normal salt solution containing the growth from 20 c.c. of ascites-dextrose broth culture 756.3 (Monkey 18, teeth).   This was a second subculture of the culture injected September 16.

November 2: Had remained well.   Blood for serum removed from saphenous vein (compare Monkey 37).

November 3: Etherized, and 1 c.c. of Virus 751[5] injected into left frontal lobe.

November 19 (sixteenth day): Irritable and tremulous, with weakness of legs.

November 20: Flaccid paralysis of both legs.   Wrist-drop on right.

November 26: Right arm and back muscles gone.   Left arm weak and ataxic, but could be used to take food.   Good appetite.

December 5: Improving; able to sit up.   Arms were stronger, but markedly ataxic.   Legs could be moved a little.

December 15: Got about quite well.   Legs paretic and began to show contractures.

EXPERIMENT 5.—*A monkey injected intracerebrally with filtrate of brain and cord of a monkey which did not have pathologic lesions of poliomyelitis was not immune to test virus.*—Monkey 24, M. rhesus, 2.3 kilos.

Previous inoculation, October 5.   Etherized and 1.5 c.c. of Berkefeld N filtrate of Virus 737[2] (glycerinated brain and cord of Monkey 16) injected into left frontal lobe.   (Monkey 16 was inoculated with a filtrate of mixed human and monkey virus and developed muscular weakness, but microscopic sections did not give the picture of experimental poliomyelitis.)

November 3: Had remained well.   Etherized, and 1 c.c. of Virus 751[5] injected into left frontal lobe.

November 10 (seventh day): Irritable, with rapid tremor of neck and shoulder muscles.   Internal squint, apparently due to weakness of right sixth nerve.   General muscular weakness.

November 13: Markedly ataxic.   Left arm awkward.

November 17: Less tremor.   Both arms weak, especially the right, which showed complete wrist-drop.   Right leg tired quickly.   No knee-jerk on right.   Strabismus less marked.   Photophobia.

November 26: Improving.   Shaky and weak; took food well.

December 15: Very active: showed only some residual weakness of right arm; slight internal strabismus and photophobia.

EXPERIMENT 6.—*Example of apparent immunity conferred by inoculation with filtrate and virus seven weeks previously, without evidence of infection.*—Monkey 17, M. rhesus, 2.5 kilos.

Previous inoculation, September 13.   Etherized.   Injected into fron-

tal lobe 1.5 c.c. of Virus 737 (compare Monkey 24) which had been passed through a dense porcelain filter.

September 19: Had remained well. Etherized, and 0.75 c.c. of fresh human virus 729 injected into frontal lobe.

November 3: Had remained well. Etherized, and 1 c.c. of Virus 751[5] injected into left frontal lobe.

December 15: Had continued to be perfectly normal.

EXPERIMENT 7.—*Example of apparent immunity conferred by inoculation with virus from two monkeys which were paralyzed with virus and culture from a paralyzed rabbit.*—Monkey 14, M. rhesus, 2.1 kilos.

Previous inoculation, September 11. Etherized and 1.5 c.c. of a Berkefeld filtrate of fresh emulsion of brain of Monkey 19 (see below) injected into frontal lobe.

September 18: Right arm used rather awkwardly. No other symptoms.

September 20: Well; no weakness of right arm detected. Etherized and 1 c.c. of emulsion of glycerinated brain and cord of Monkeys 10 and 12 injected into frontal lobe. (Monkey 10 received an intracerebral injection of an emulsion of brain of Rabbit 1017; Monkey 12[7] was twice injected intravenously with a pure culture of streptococci grown from the brain of Rabbit 1017. This was the third of a series of rabbits in which a strain of streptococcus recovered from the brain of a patient who died of poliomyelitis caused flaccid paralysis. Both monkeys came down with flaccid paralysis, and microscopic sections showed marked cord lesions, without, however, the perivascular infiltration which is considered typical of experimental poliomyelitis in monkeys.)

November 3: Had remained well. Etherized and 1 c.c. of Virus 751[5] injected into left frontal lobe.

November 17: No symptoms.

December 15: Had remained well.

EXPERIMENT 8.—*Example of apparent immunity conferred by intracerebral injection of a culture of streptococci isolated from a human cord.*—Monkey 19, M. rhesus, 2.8 kilos.

Previous inoculation, September 16. Etherized and 1.5 c.c. of suspension of Culture 707.2 injected into frontal lobe. (This strain came from a single colony of pleomorphic streptococci 2 cm. from the top of a four-day ascites-dextrose-agar shake culture of an emulsion of fresh spinal cord from a patient who died of poliomyelitis. This colony was subcultured in tubes and bottles of ascites fluid plus sterile rabbit kidney, and ascites broth plus sterile kidney. September 16 these subcultures had been growing twenty-three days, and smears showed an extremely pleomorphic organism; lanceolate diplococci, round cocci in short chains, flat-sided meningococcus-like diplococci, and very small globoid chains. Chains could be found in which each of these types was present. On

aërobic blood-agar plate these cultures grew pure as fine, dry, green-producing colonies.)

September 17: Sick since injection; quiet, would not eat. No muscular weakness.

September 18: Better; began to eat. Arms and legs strong; reflexes normal.

October 2: Had remained well.

November 2: Had remained well. Blood removed from saphenous vein.

November 3: Etherized and 1 c.c. of Virus 751⁵ injected into left frontal lobe.

December 15: Daily observations had shown no abnormality.

COMMENT

Three unused and five used monkeys were injected with a monkey virus. The test virus had been carried through monkeys to a stage of virulence at which it should, according to the experience of investigators, cause experimental poliomyelitis in all non-immune monkeys injected. The two control monkeys became severely paralyzed and were killed. The third (Monkey 37) also became a good control, as the experiment proved that the animal from which 70 per cent. of the serum was obtained was not an immune monkey (Monkey 21).

Monkeys 21 and 24, which came down with typical poliomyelitis symptoms and recovered, are of considerable interest in that they show that inoculation with cultures or filtrate of virus from non-poliomyelitis sources, as determined by pathologic findings, does not confer immunity to a virulent virus.

There remain the three monkeys which showed no symptoms following the test injection and were normal forty-five days after. The question whether or not these animals showed any symptoms of infection after their previous inoculation is difficult to determine. Monkey 14 had a definitely clumsy right arm for about twenty-four hours at a period seven days after his first injection, but no weakness could be made out. His awkwardness rapidly disappeared, and he showed none of the usual symptoms of irritability and tremor. No symptoms were observed in the other two monkeys.

The important point of the experiment is that two of the three monkeys which were not affected by the test virus had previously been injected with material obtained from cultures of human poliomyelitis nervous tissue. Monkey 14 received filtrate and emulsion of brain and

cord of monkeys that had been paralyzed with rabbit virus and culture; the successive passages of this strain through three rabbits in the form of large, lanceolate diplococci grown aërobically would seem to exclude any possibility that the small anaërobic organism described by Flexner and Noguchi could have been carried over. Similarly, the culture used in Monkey 19 came from a single colony near the top of an agar shake culture. Flexner and Noguchi[4] state that they have never obtained from poliomyelitic material in solid medium an initial growth of the small organism, aside from contaminations.

We wish to record these observations as suggestive of the importance of immunologic studies with the pleomorphic streptococcus which has been isolated from the central nervous system of cases of human and experimental poliomyelitis.

STUDY III.—BACTERIOLOGIC OBSERVATIONS IN EXPERIMENTAL POLIOMYELITIS OF MONKEYS *

EDWARD C. ROSENOW AND EDWARD B. TOWNE

In a previous report[7] we stated briefly the cultural characteristics of a pleomorphic streptococcus isolated from the brain and cord of cases of poliomyelitis in man. We have now studied the bacteriology of the central nervous system of ten monkeys that succumbed to experimental poliomyelitis.

Fig. 361 shows graphically the history of this series of animals, of which 8 were M. rhesus, one was M. sinicus, and one was Ceropithecus sabeus. The virus was passed from one monkey to the next as a 5 per cent. emulsion in normal salt solution of glycerinated or fresh brain and cord or as a filtrate of such an emulsion. The animals were put under ether anesthesia, and a dose averaging 1 c.c. was injected into the frontal region of one of the cerebral hemispheres. Monkeys 28, 40, and 46, which were injected with filtrate, received, in addition to the intracerebral inoculation, an injection of 10 c.c. of filtrate into the peritoneal cavity.

Each of these monkeys showed to a greater or less degree the usual symptoms of experimental poliomyelitis—excitement, tremor, and paralysis. Most of them were prostrate when killed, but two were etherized and necropsied when it became evident that they were re-

covering from abortive attacks of the disease.   Microscopic sections of brain and cord gave the typical picture of experimental poliomyelitis in each of the animals.

The necropsies were done under rigid aseptic precautions. Emulsions ground up in a sterile air-chamber or fragments of the brain, cord, and intervertebral ganglia were transferred immediately into culture-mediums.

METHODS OF CULTIVATION

Many types of culture-mediums were employed successfully. Of these, the following were the more important:

1. Ascitic-dextrose broth, made with Witte peptone and Liebig's
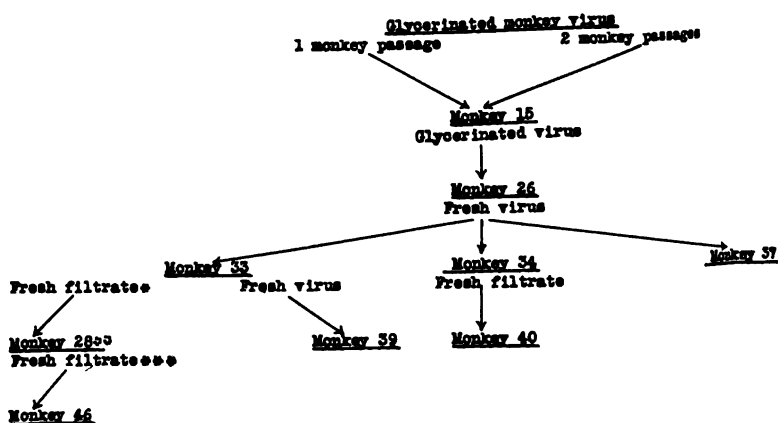
Fig. 361.—Diagram showing derivation of material used to paralyze ten monkeys.

extract of beef, titrated to 0.6 to 0.8 per cent. acid to phenolphthalein, and containing dextrose 0.2 per cent. and ascitic fluid 10 per cent.

2. Ascitic broth, as above, without the dextrose.

3. Ascitic-dextrose agar containing 1 per cent. dextrose and 2.5 per cent. agar.

4. Unheated and unfiltered ascitic fluid.

5. Steamed ascitic fluid.

6. 1.5 per cent. agar (2 parts) + ascitic fluid, ascitic-dextrose broth, or ascitic broth (1 part).

7. Plates made of agar and fresh human blood.

8. Slants of similar blood-agar—aërobic and anaërobic.

The ascitic fluid and the ascitic agar were used in tall tubes to which fresh sterile rabbit kidney and a layer of sterile mineral oil were added, according to the methods described by Flexner and Noguchi.[4] The column of medium measured 0.8 cm. in diameter and 13 cm. in height. The heated ascitic fluid in similar tubes was steamed for thirty minutes in the Arnold sterilizer after addition of sterile kidney or liver. The tall tubes were also employed for ascitic-dextrose broth, ascitic broth, ascitic-dextrose-broth agar, and ascitic-broth agar. To these were added sterile tissue and mineral oil, or one or both might be omitted.

Test-tubes taking a column of medium 1.5 cm. in diameter and 9 cm. high were also employed for ascitic-dextrose broth, ascitic broth, and ascitic-dextrose agar. These will be called short tubes. Sterile tissue and oil might be added, but one or both were usually omitted. Six-ounce nursing-bottles, containing 150 c.c. of fluid in a column 4.5 cm. wide and 8.75 cm. high, were used for ascitic-dextrose broth or ascitic broth, with or without sterile tissue and always without oil.

To obtain the initial growth three mediums were regularly used: (1) Tall tubes of ascitic fluid plus sterile tissue and oil; (2) ascitic-dextrose broth in (a) tall tubes plus tissue and oil; (b) short tubes with or without sterile tissue; and (c) bottles with or without tissue; and (3) ascitic-dextrose agar, usually without tissue. Forty to 50 tubes and bottles, with controls, were inoculated with central nervous tissue at each necropsy. Subcultures were made to any of the mediums, and all tubes were frequently controlled by plating; further subcultures were often made from single colonies on the plates. The cultures were incubated at 35° C.; only a few were put in the anaërobic jar, as it was thought desirable to make daily smears of all cultures which grew.

CULTURAL RESULTS

A streptococcus identical with the one obtained from poliomyelitis in man was isolated from the central nervous system of each of the ten monkeys. Three other monkeys which did not have poliomyelitis gave completely negative cultural results. The number of pure cultures obtained from a monkey varied considerably through the series. Approximately 50 per cent. of the cultures were sterile; of the remainder, about 15 per cent. showed contaminations only, 15 per cent. showed the characteristic diplococcus and also contaminations, while the remaining 20 per cent. contained the streptococcus in pure culture. Tubes inoculated with fragments or emulsion of cerebrum were usually pure cultures of strep-

tococcus or sterile, as this was the tissue which could be obtained with the least risk of contamination by air bacilli.

Cultures in similar mediums of blood or spinal fluid, and of emulsions of heart muscle, liver, spleen, and kidney, were always sterile. In a few instances green-producing streptococci were isolated from lymph-glands.

In aërobic bottles or short tubes of broth, with or without tissue, a diffuse turbidity appeared in twenty-four to forty-eight hours. Those inoculated with emulsion grew more often than those inoculated with fragments. Smears at this time (Fig. 362) showed elongated diplococci, often in short chains and occasionally in long chains. Giemsa stain frequently brought out a narrow clear zone about the organism which suggested a capsule; in a few instances this zone took a definitely red color. Subcultures on blood-agar plates invariably gave a growth of small, dry, green-producing colonies, which might be surrounded by a narrow, hazy zone of hemolysis, especially after forty-eight to seventy-two hours' incubation. In shake cultures of the emulsions in short tubes of ascitic-dextrose-agar small, discrete, grayish colonies appeared in the deeper portion of the medium usually on the second or third day.

As was pointed out by Flexner and Noguchi, the best medium in which to obtain the small globoid form was unheated ascitic fluid in a tall column to which fresh sterile rabbit kidney and oil were added. These cultures grew better when inoculated with fragments of nervous tissue rather than emulsions. Similar tall tubes of ascitic dextrose and ascitic broth plus tissue and oil grew less frequently, and the organism was more apt to die after a few days of growth.

We will now consider the growth obtained in the initial cultures of ascitic fluid plus sterile tissue and oil. All tubes were examined twenty-four, forty-eight, and seventy-two hours after inoculation: if any organisms were found in the smears, those tubes were examined daily thereafter. With a long fine pipet a small amount of medium was drawn from near the bottom of the tube and two or three smears were made. As a routine two of these were stained by the rapid and slow Giemsa methods described by Flexner and Noguchi, and sometimes a third was stained by Gram's method. From the same pipeted specimen plates and other subcultures were made.

In all tubes which did not remain permanently sterile organisms were demonstrated in the smears made during the first forty-eight hours after inoculation—usually on the first day, but occasionally not until

the second.   These organisms were always similar to those found at the same time in aërobic broth cultures of the same material.   They were usually elongated diplococci, occurring as pairs and short chains (Figs. 365, *a*, and 366, *a*) or in long chains (Fig. 363, *a*).   There was almost always a clear zone around the diplococci, suggesting a capsule; in a few instances the Giemsa method stained a capsule, making the diplococci appear larger and somewhat irregular (Fig. 364).   In these smears there were frequently cocci, sometimes singly, but often in chains, which showed early transverse fission, giving as a result a diplococcus resembling a meningococcus with flat sides opposed (Figs. 367, *c*, and 367, *d*). The ascitic fluid medium was at this time absolutely clear throughout.

After the day on which the initial growth was first found there was a

Fig. 362.—Twenty-four-hour culture in ascitic-dextrose-broth bottle plus emulsion of lumbar cord. Rapid Giemsa (× 1000).

wide limit of variation in the type of growth.   The tendency was for the organisms to grow smaller by a process of fission.   In some cases the change was slow; sometimes there were three or even four weeks before the microörganisms were all of globoid size (*i. e.*, 0.15 to 0.3 μ).   Figs. 365, *a*, 365, *b*, and 365, *c*, are examples of such a tube; in these instances the medium began to grow hazy about the tissue on the sixth to eighth day, the slight cloud rose slowly through the lower third or half of the column, reaching its height about the end of the second week.

More frequently the time required for a culture to grow down to globoid size was from five to ten days.   Such tubes were hazy at the bottom about the fifth to the seventh day.   The mechanism of the change in all tubes which showed a pure culture of small forms in six

or more days appeared to be one or more transverse divisions of the individual cocci in the chains.

Tubes in which a haze appeared earlier—on the third or fourth day—

Fig. 363.—Ascitic fluid plus tissue and oil, inoculated with fragment of cervical cord. To show breaking down by division in two planes. a, Twenty-four hour smear. Rapid Geimsa (× 1000). b, Forty-eight-hour smear. Slow Giemsa (× 1000). c, Forty-eight-hour smear. Chain of large diplococci; transverse and longitudinal division of one diplococcus into four pairs of diplococci, and clumps of the results of similar division. Slow Giemsa (× 1000).

exhibited a much more rapid decrease in the size of the organisms, and rarely showed a pure culture of globoid size. The individual cocci divided transversely and then longitudinally, so that one large diplococcus broke into four small diplococci (Fig. 363, c). The resulting cocci have

been seen in process of dividing transversely once more, but this could not be photographed. In such a tube, on the second or third day, every size might be seen in the same field—lanceolate diplococci, flat-sided diplococci, small cocci in clumps of four or eight, and very small globoid-size diplococci. Rarely such a tube showed pure globoid bodies on the fourth to sixth day, but usually larger organisms were present. A second cycle has been observed in these tubes: larger forms gradually appeared after the fourth to the eighth day up to about the fourteenth day, when these began to divide and grow smaller again, becoming entirely small forms about the fifth week. However, this was an infrequent occurrence, and it was the rule for such tubes to show both large and small forms indefinitely.

Fig. 364.—Ascitic fluid plus tissue and oil: First subculture from similar tube inoculated with fragment of cerebrum. Twenty-four hours. Excapsulated lanceolate diplococci, some of which have divided transversely. Rapid Giemsa ($\times$ 1000).

Occasionally the capsule of the organism took the Giemsa stain deeply enough to obscure the size of the diplococci. When this occurred, it was true with both the slow and rapid Giemsa methods, except in one instance. Throughout this series, of which examples from the first to the fourteenth day are shown, the smears stained by the rapid method showed a faint zone about the diplococci, while the smears made from the same pipet and stained by the slow method showed a capsule which held the stain strongly (Figs. 366, a–366, f).

Subcultures were made on blood-agar plates at frequent intervals. As long as there were large organisms in the tubes, a growth of small, green-producing colonies occurred on the plates. When only small globoid forms were present, there was no growth on the plate. Stab

'16—53

soon extended to the top. Such transplants were especially favorable for studying the mechanism of fission, for in a smear of a twenty-four-hour culture all stages could be demonstrated (Figs. 367, a–367, d).
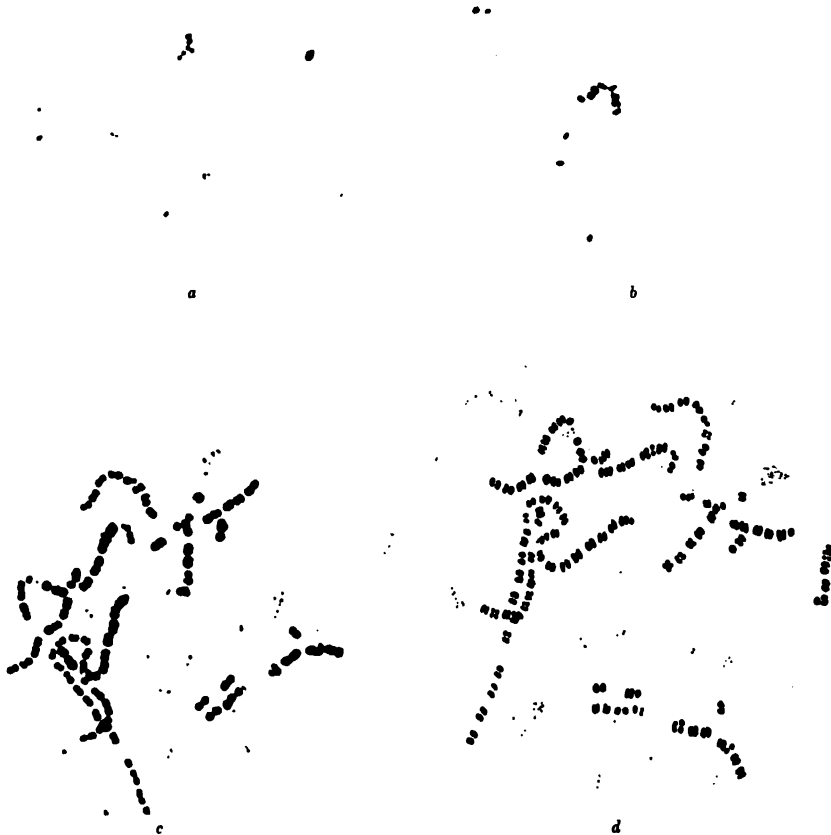
Fig. 367.—Ascitic tissue fluid subculture from similar tube inoculated with fragment of cervical cord. Twenty-four-hour rapid Giemsa smears. a, Stage in breaking up of a diplococcus. The upper pair are the result of transverse division; the lower pair have undergone longitudinal division also, and the lowest resulting diplococcus has swung 90 degrees from its neighbor (× 1000). b, Double fission of two diplococci into eight diplococci (× 1600). c, To show all stages: Lanceolate diplococci undergoing transverse fission into flat-sided diplococci. Further longitudinal fission and resulting small forms. Clear spaces in chains which contain small, irregular, reddish masses (× 1000). d, Camera lucida drawing to show further details of c.

Cultures in ascitic fluid plus tissue and oil which showed only globoid bodies, and which would not grow in aërobic broth or on a plate, were grown back to large lanceolate diplococci without difficulty if they were
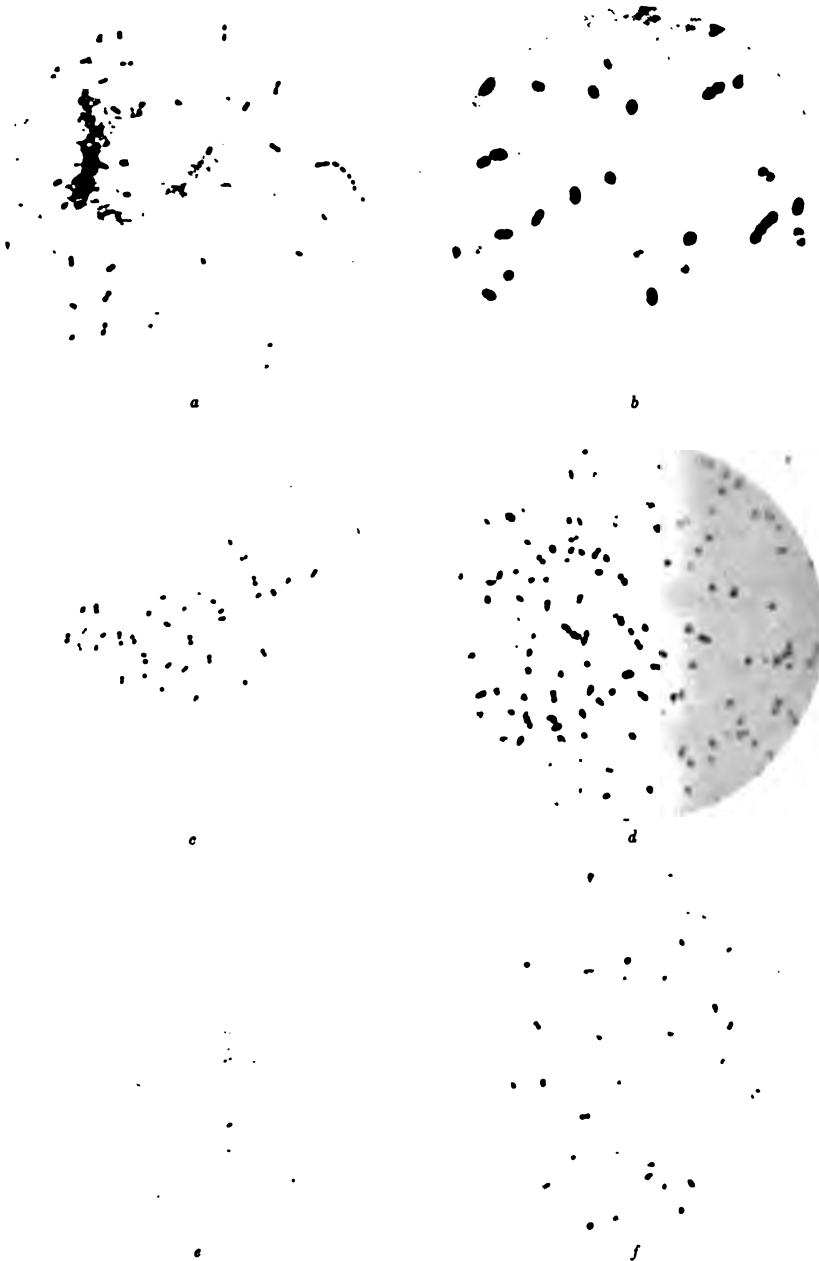
Fig. 366.—Ascitic tissue fluid inoculated with fragment of brain. To show slow diminution in size and staining of capsule by slow Giemsa method, while smears from the same pipet stained by rapid method do not show a distinct capsule. a, Twenty-four hours. Rapid Giemsa (× 1000). b, Twenty-four hours. Slow Giemsa (× 1000). c, Four days. Rapid Giemsa (× 1000). d, Four days. Slow Giemsa (× 1000). e, Fourteen days. Rapid Giemsa (× 1000). f, Fourteen days. Slow Giemsa (× 1000).

unheated ascitic fluid plus tissue and oil, and in this medium after ster-
ilization in the Arnold sterilizer, but not usually in other mediums.
By methods similar to those described above cultures of the filtrates
were grown up to the large form.

It was noticed that in tubes which were contaminated with B. sub-
tilis the diplococci became small rapidly and tended to remain small.
Subcultures of several strains were inoculated with B. subtilis; Figs.
368, a, and 368, b, show the typical result of such experiments. In the
nine-day smears the contaminated tube showed only globoid chains,
while the uncontaminated control showed the pleomorphic organism
in different stages of division.

The tendency to break down to small forms under proper cultural
conditions was not peculiar to the diplococcus isolated from poliomye-
litis material. Strains of pneumococci and streptococci from various
sources have been planted in ascitic fluid plus tissue and oil; some of
them have gone through precisely the same changes, and in two instances
they have been passed through a Berkefeld N filter and grown large
again. Fig. 369 shows various stages of division with resulting globoid-
size organisms in a culture of a five-year-old pneumococcus isolated
from the blood during life in lobar pneumonia and which had passed
through 35 animals. This strain had always killed the animals by
pneumococcemia. It had been in dried mouse spleen in a sealed tube
in the dark for three years at room temperature. Before inoculation of
the tube from which a smear is shown it had been subcultured twice
from single green colonies on blood-agar plates.

DISCUSSION

On examining again preparations made from cultures of central
nervous system of cases of human poliomyelitis it is now possible to
place the various forms—lanceolate diplococci, rounder cocci, and espe-
cially the "rather large oval cocci staining a pinkish tint with the
Giemsa stain"—which we described in the previous report. Flexner
and Noguchi noted in old cultures "enlarged and irregularly stained
bodies" which they considered were probably degenerations. They
also described a faintly tinted or colorless zone which sometimes sur-
rounded the globoid organisms.

The diplococcus isolated from the central nervous system and in-
tervertebral ganglia of ten monkeys which were given experimental
poliomyelitis by means of an adapted virus remains an ordinary-sized

diplococcus under aërobic conditions. Sometimes a capsule is demonstrable. Under conditions of low oxygen tension the same organism may appear in twenty-four- or forty-eight-hour cultures in ascitic fluid plus tissue and oil. Many factors appear to play a part in determining the type of growth after this. With a suitable specimen of ascitic fluid and fresh sterile tissue, and with a scant initial growth, the organisms become small slowly by transverse fission. In such tubes there may be a pure growth of globoid organisms after five to fifteen days. The medium is clear, while large forms are present. With similar medium and larger initial growth, especially in subcultures, the fission is first transverse and then longitudinal, and the resulting cocci go through further division. Such tubes become turbid early—second to fourth day—and all sizes of the organism may be found in early smears. These tubes seldom become pure cultures of globoid bodies, but they may go through a second cycle of division and become pure small forms. Sometimes there is a demonstrable capsule in all stages of division.

If the ascitic fluid is not suitable, if the tissue is not fresh, or if fluid and tissue are steamed, division takes place slowly if at all, and pure globoid cultures may not be obtained. When such tubes are inoculated with B. subtilis, sufficiently anaërobic conditions are obtained to cause fairly rapid division, with resulting pure globoid cultures in some instances.

Thus it appears that an explanation of these phenomena might be based on a consideration of colloid chemistry. If there are so many large diplococci that their oxygen requirements cannot be satisfied by the medium, division which gives more surface for the same sized body would allow a certain number of the resulting smaller organisms to survive. When an abundant growth of large diplococci is thus forced to break down rapidly, so many of the small forms may die that those which survive receive more oxygen than is necessary, because the diffusion through the oil is greater than the consumption, and they may then grow larger (second cycle). Similarly, a pure culture of globoid size after passage through a Berkefeld N filter will grow large if provided with more oxygen than is necessary to keep them in a small form. It may readily be imagined that similar fissions give ultramicroscopic forms which may be the organisms which pass through a filter.

Under exactly right conditions of medium, tissue, and size of inoculation it is conceivable that nothing but small globoid organisms would be found as early as the third or fourth day. Occasionally such a tube

does occur, but it has always contained large forms on the first or second day or on both. If each tube is not examined daily for three days, this stage may be overlooked. Such tubes do not show any clouding of the medium until the globoid forms are well established on the fourth to sixth day. Cultures which have been under anaërobic conditions for some time are much more liable to grow in this fashion than are initial cultures; but in all of them forms well above globoid size may be seen in smears made on the first or second day.

This method of growth in accordance with the oxygen tension of the medium is not peculiar to the diplococcus isolated from poliomyelitis nervous tissue, but may be demonstrated, even to growth after filtration, by the use of streptococci and pneumococci from various sources. It, therefore, appears that similar methods may give valuable information if applied to the study of other diseases caused by a filterable organism or virus.

CONCLUSIONS

The small globoid microörganism which Flexner, Noguchi, and their co-workers have proved to be the cause of experimental poliomyelitis has always, in our experience, been the result of the breaking down of large diplococci, which have been isolated from the central nervous tissues of each monkey infected with experimental poliomyelitis. These organisms have not been isolated from other tissues except lymph-glands of poliomyelitic monkeys, nor from any tissue of normal monkeys. The mechanism by which the large forms become small has been demonstrated.

REFERENCES

1. Landsteiner, K., and Levaditi, C.: "La transmission de la paralysie infantile aux singes," Compt. rend. Soc. de biol., 1909, lxvii, 592–594.
2. Flexner, S., and Lewis, P. A.: "The Nature of the Virus of Epidemic Poliomyelitis," Jour. Amer. Med. Assoc., 1909, liii, 2095.
3. Wickman, I.: "Acute Poliomyelitis," Nervous and Mental Diseases Monograph Series 16, New York, 1913, p. 6.
4. Flexner, S., and Noguchi, H.: "Experiments on the Cultivation of the Micro-Organism Causing Epidemic Poliomyelitis," Jour. Exper. Med., 1913, xviii, 461–485.
5. Rosenow, E. C.: "Elective Localization of Streptococci," Jour. Amer. Med. Assoc., 1915, lxv, 1687–1691; "Elective Localization of Bacteria in Diseases of the Nervous System," Ibid., 1916, lxvii, 662–665.
6. Mathers, G.: "Some Bacteriologic Observations on Epidemic Poliomyelitis," Jour. Amer. Med. Assoc., 1916, lxvii, 1019.
7. Rosenow, E. C., Towne, E. B., and Wheeler, G. W.: "The Etiology of Epidemic Poliomyelitis; Preliminary Note," Jour. Amer. Med. Assoc., 1916, lxvii, 1202–1205.

TUMORS OF THE SPINAL CORD: WITH A REPORT OF EIGHTEEN CASES *

EMIL H. BECKMAN

In reviewing the literature on the subject of tumors of the spinal cord one is impressed by the large number of instances in which a diagnosis was made at autopsy and the comparatively few reports of early diagnosis and operation. This is rather surprising when we consider that the condition is a disease in which the pathologic lesion is a neoplasm whose existence and growth mean a destruction of the delicate structures of the spinal cord. There is no argument for delaying operation after a definite diagnosis has been made. It is probable, however, that in a great many instances in which such a diagnosis is suspected no operative means for relief is undertaken. This is due to the fact that an absolute diagnosis is often impossible and to the fear of a fatal termination following laminectomy.

In our work in this field we have found that many persons with cord tumors do not present the classic symptoms described formerly. Neurologists have concluded that disturbance of the tactile sense is necessary in order to make a diagnosis of tumor of the spinal cord. One prominent authority states that he knows of no recorded instance of cord tumor in which this symptom was absent. In one case of our own in which the tumor lay on the anterior surface of the cord there was no disturbance of tactile sense. In this case the location of the tumor was made entirely from the disturbance of pain and temperature sense.

Root-pains were previously supposed to be absent in cases of intramedullary tumors; however, they were one of the prominent symptoms in each of five consecutive cases during the past year. We have found that when a careful history is elicited, root-pains are certainly one of the commonest and most persistent symptoms in tumors of the spinal cord. They vary greatly in individual cases; they are not always constant or

severe in character, and in many instances an interval of several weeks or months may intervene between the attacks. In a recent case of extra-medullary tumor the pain was intermittent in character, but extremely intense when it did occur. During the attacks the patient had spells of vomiting. The pain was unilateral and confined to the region of the gallbladder. An operation on the gallbladder had been performed during one of the seizures. Later on the same pain returned with increased intensity, accompanied by paralysis of the lower extremities. A tumor was found lying on the posterior surface of the cord and pressing on the right seventh dorsal nerve-root. It would be interesting to know whether root-pain may be intense enough to cause reflex vomiting without disease of the abdominal viscera.

In suspected cases of spinal-cord tumor laminectomy is often not advised on account of the fear of a high mortality following such procedure. In the past few years the advance in neurologic surgery has been as great as, and possibly even greater than, that in the field of general surgery. The mortality following laminectomy for spinal cord disease should be well under 10 per cent.

In a series of 43 consecutive operations for spinal-cord disease exclusive of traumatic cases we have had 4 deaths. One of these might be classified as accidental. The patient died on the eleventh day of pulmonary embolism. The autopsy revealed a large number of clots in both iliac veins and an enormous number of clots in the pulmonary vessels. Death was instantaneous. Another death was that of a patient with a tuberculous lesion in front of the dura and extensive tuberculous lesions of both adrenals. Death resulted from suppression of urine on the fifth day. The cause of death in the other two cases was not absolutely determined, but it certainly was not shock.

I believe that in many questionable cases with level symptoms and paralysis, even though a definite diagnosis of tumor cannot be made. a laminectomy is justifiable. A sufficient number of such patients will be benefited to justify the procedure, and in some a tumor will be found. Certainly a patient whose chance for recovery is slight with any other form of treatment should not be denied the privilege of an exploratory laminectomy. Some authorities have even advised laminectomy with incision of the dura for the purpose of decompression in degenerative conditions of the cord. Our experience would lead us to believe, however, that this operation is hardly justifiable, although we have one patient who entirely recovered from paralysis following a negative exploration.

A few cases of localized syringomyelia with a single cyst or collection of fluid in the central canal of the cord have been entirely relieved of symptoms when the cyst was evacuated.   At least two such cases were reported by the late Dr. Monroe, and a few others have been reported in the literature.

In two instances we have operated on cases of this kind.   The cord collapsed after the cyst was punctured and resumed its normal shape, but the relief of symptoms was not marked in either instance.   It is

Fig. 370.—Tuberculoma lying on the anterior side of the dura and compressing the cord.

Fig. 371.—The same as Fig. 370.   The dura incised through the tuberculoma.

quite likely that in some of these cases there are more than one of these cysts situated at different levels of the cord.

In cases of angioma of the cord with a large mass of dilated vessels causing pressure patients are often entirely relieved by a simple decompression of the spinal cord.   As more experience is obtained it may be found justifiable to perform this operation in other types of cases. The present report is based on 18 consecutive cord tumors.

1. *Extradural Tumors.*—Extradural tumors are comparatively rare, and in most instances are not true tumors of the spinal cord.   They are sarcomas, fibromas, lipomas, or tuberculous processes which have no

Fig. 372.—Destruction of vertebral arches and spines due to pressure from an extradural fibroma.
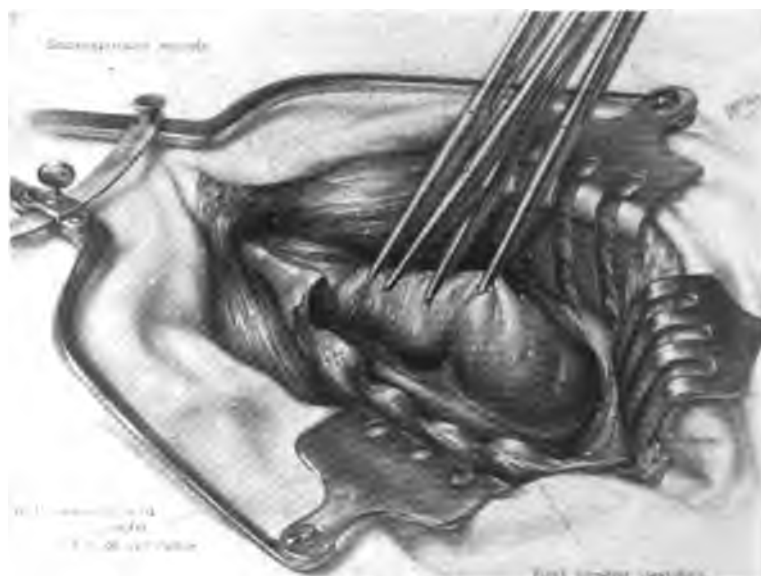
Fig. 373.—Large extradural fibroma compressing the cord and causing complete paralysis.

direct connection with the spinal cord. They produce cord symptoms
from pressure because they happen to be situated within the arches of
the spine and press on the dura and cord. A few tumors which arise
from the dura itself produce symptoms in the same manner, either within
or without the neural canal. In this series there were two tumors of this
class. One was a tuberculoma situated on the anterior surface of the
dura and pressing backward on the cord (Figs. 370 and 371). It had
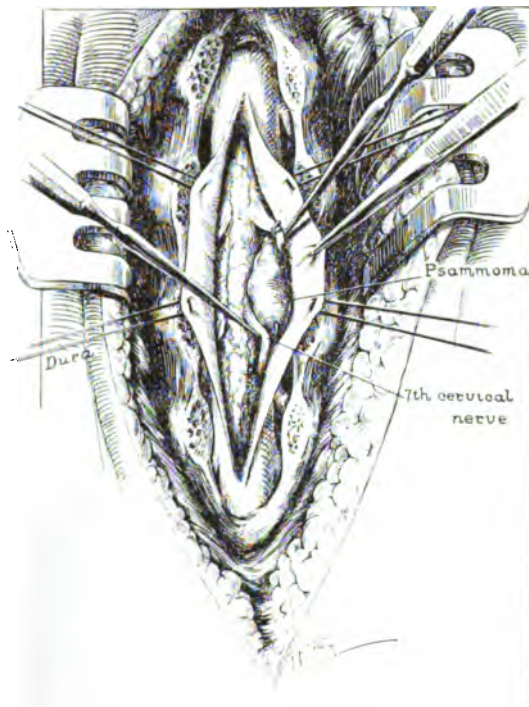
Fig. 374.—Tumor lying on the anterior side of the cord in the cervical region, presenting between the sixth
and seventh cervical nerves.

not, however, involved the structures of the dura. At operation the
cord bulged out of the canal when the dura was opened, although no
tumor could be found on the anterior surface of the cord or attached to
the dura. Autopsy revealed this tuberculous mass, which explained the
cord symptoms. The other was a large fibroma lying within the arches
of the spine and producing enough pressure to erode three laminas and
spinous processes and to cause paralysis by flattening the cord (Figs.
372 and 373). Unfortunately, the patient had been told two and a

half years previously that her trouble was degeneration of the cord, and that it was useless to have anything further done. Even though the pressure was great enough to erode the bone in a marked degree and to cause complete paralysis by compression of the cord, there was absolutely no history of pain.

2. *Intradural Extramedullary Tumors.*—These are the commonest type of cord tumors. A large number of them are sarcomas or gliomas, the two often being confused. Fortunately, a large percentage of them lie on the posterior surface of the cord, are readily seen when the dura is opened, and in most instances can be easily removed from the surface of the cord, the attachments being mostly filmy adhesions between the
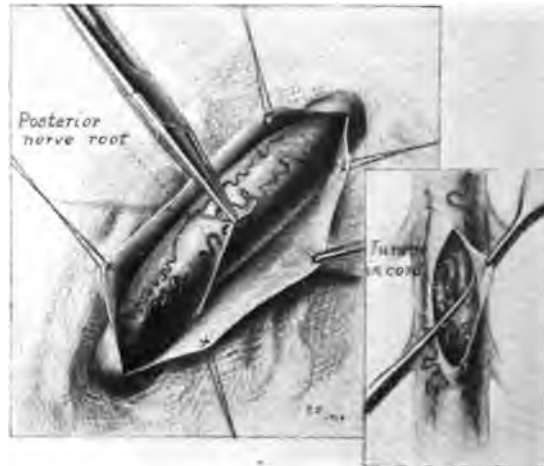
Fig. 375.—Intramedullary tumor of the cord. Appearance before and after incision into the cord.

tumor and the pia. The series here reported included six tumors of this character (Fig. 374).

3. *Intramedullary Tumors.*—These tumors are mostly gliomas, are situated within the substance of the cord, and were formerly supposed to be inoperable, with no hope of the patient's recovery following their attempted removal. It has been found in recent years that many have a distinct capsule with a line of demarcation between the tumor and the cord substance, and that some of them can be enucleated with almost no traumatism to the cord except that consequent to the initial incision over the tumor (Figs. 375, 376, and 377). These are the cases in which the two-stage operation is often indicated. It has been found, largely

through the work of Elsberg, that if the dura is incised at the primary operation, a longitudinal incision being made through the cord substance down to the tumor, the intramedullary pressure may cause the tumor to extrude itself to such a degree in a period of ten to fourteen days that its removal can be accomplished very readily. However, this does not al-

Fig. 376.—Appearance of intramedullary tumor before incision into the cord.

Fig. 377.—Appearance of the same tumor at the second-stage operation. Tumor partly extruded from the cord.

ways occur. In one of our cases of this type the tumor was not extruded in the second stage to any considerable degree. There were six tumors of this type, four of which could be removed. In the instances in which the tumor could be removed the patients, while not by any means well, are much improved.

4. *Angioma of the Cord.*—In some cases in which the symptoms indi-

cate a tumor of the spinal cord a laminectomy has revealed a mass of
dilated blood-vessels resembling an angioma and causing pressure on
the cord.   In a few instances angiomas have been found in the corre-
sponding segment on the surface of the body (Figs. 378, 379, and 380).
Some of these patients have been entirely relieved when the pressure was
removed on opening the dura.   In other instances relief has been ob-
tained from ligation of some of these large vessels.   Our series includes
two cases of this type.   In one of them the vessels were comparatively
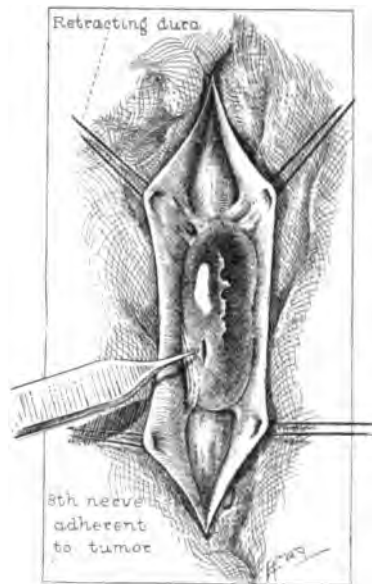
Fig. 378.—Angiomatous tumor. Appearance
when the dura was opened. Eighth dorsal nerve-
root (left) stretched across the tumor. (This pa-
tient had had his gallbladder drained during an
attack of root-pain.)
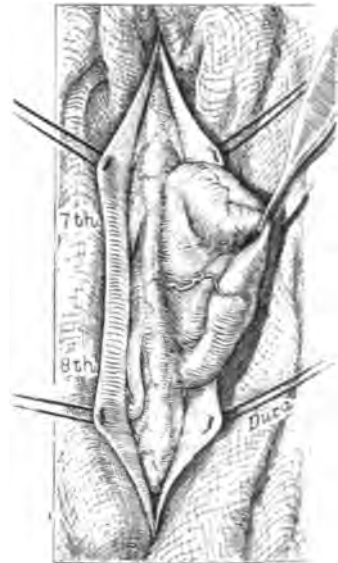
Fig. 379.—The same tumor partly elevated
from the cord, showing a single large vessel sup-
plying blood to the angioma.

small, and relief from opening the dura should have given the cord room
to expand and thus relieve the symptoms.   Unfortunately in this case
no relief was obtained.   In the other case, which has been reported
previously, the vessels were of enormous size and entirely filled the neural
canal.   Though this appeared to be the least favorable of the two men-
tioned, we were surprised to find that the patient, who had been unable
to walk before the operation, recovered so rapidly from his paralysis that
he was able to walk across the room without assistance in six weeks and
to return to his labor as a boxmaker in six months.

5. *Cysts of the Central Canal (Localized Syringomyelia. Localized Meningitis).*—We have known for a long time that there were localized accumulations of fluid in the central canal of the cord in some of the degenerative processes. Formerly none of these cases was considered
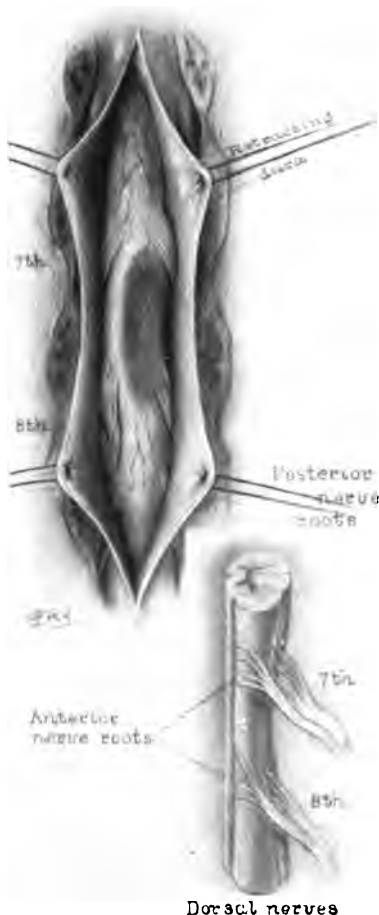
Fig. 380.—Appearance of the cord after the removal of the tumor.

surgical. Several cases have been reported in which patients with definite indications of tumor of the cord have shown at operation a single cyst in the center of the cord which produced enough pressure to cause paralysis. When a cyst of this kind is evacuated, the cord collapses and resumes its normal shape and size. If there happens to be but one of

'16—54

SPINAL CORD TUMORS

	Case	Sex	Age	Duration of Symptoms	Location of Tumor	Time since Operation	Pathologic Diagnosis	Unimproved	Improved	Well	Dead	Cause of Death
Extradural	142,990	F	90	4.5 yrs.	Lumbar	1 yr.	Fibroma		+		+	Suppression of urine; tuberculous adrenals
	125,886	F	59	1 yr.	Dorsal	..	Tuberculoma				+	?
Intradural (extramedullary)	91,114	F	40	9 mos.	Dorsal	..	Sarcoma					
	111,220	F	36	3 yrs.	Cervical	26 mos.	Sarcoma		?	+		
	162,179	F	27	2¾ yrs.	Dorsal	2 mos.	Glioma			+		
	155,662	M	50	4 yrs.	Dorsal	6 mos.	Angioma			+		
	154,990	F	38	1 yr.	Cervical	6 mos.	Psammoma			+		
	168,059	F	58	1.5 yrs.	Dorsal	1 mo.	Sarcoma				+	Pulmonary embolism on eleventh day
Intramedullary	152,390	M	41	1 yr.	Dorsal	7 mos.	Glioma		+			
	130,591	M	28	1 yr.	Lumbar	8 mos.	Glioma	+				
	59,174	M	39	1 yr.	Dorsal	3 yrs.	Glioma	+				
	155,615	M	43	5 yrs.	Dorsal	6 mos.	Glioma		+			
	105,671	M	17	1 yr.	Dorsal	26 mos.	Glioma	+				
	170,871	M	54	4 yrs.	Dorsal	1 mo.	Glioma		?			
Angioma	102,880	M	30	17 yrs.	Dorsal	2.5 yrs.	Angioma			+		
	122,575	F	46	1 yr.	Dorsal	20 mos.	Angioma	+				
Cysts	92,786	F	24	14 yrs.	Dorsal	3 yrs.	..		+			
	42,688	F	46	10 yrs.	Dorsal	6 yrs.	..	+				

these accumulations of fluid, recovery often follows its evacuation. If there are multiple cysts, improvement cannot be expected. The series contains two cases of this type, in one of which there was a fair degree of improvement.

6. *Giant Tumors of the Cauda Equina.*—Large tumors of the cauda equina situated about the nerves have been reported in several instances. They are often extremely large, and are difficult to remove on account of their situation among the nerves of the cauda. I have not seen any tumors of this character.

CONCLUSIONS

I believe that many tumors of the spinal cord are overlooked because the average physician is not familiar with the methods of neurologic diagnosis. In order to obtain better results with fewer cases of permanent paralysis it is necessary that these tumors be diagnosed early and operated on during the early stages. Obviously pressure maintained on the spinal cord for a considerable length of time produces a degenerative process in the delicate cord structures from which there is no regeneration. I believe that in many instances in which the diagnosis of cord tumor is not absolute, but in which there are level symptoms, a laminectomy should be advised. Root-pains are a common symptom in most cord tumors. In some instances the pain may be so slight, or the predominance of other symptoms at a later period may so overshadow the previous pain, that it is entirely forgotten by the patient and can be obtained only by the most careful questioning. Level symptoms are always present in the later stages, although tactile, pain, and temperature sense may not be involved to the same degree. In some instances one of these may be absent, and the tumor may then be located by the definite level of the others. I urge a more careful examination in neurologic conditions and a more frequent and early laminectomy in cases of suspected tumors as the only method of preventing crippling due to long-standing pressure of tumors on the cord.

MECHANICAL DERANGEMENTS OF THE KNEE-JOINT *

MELVIN S. HENDERSON

Mechanical derangements of the knee-joint are relatively common and may be due either to extrinsic causes, such as exostoses, or to intrinsic causes, such as fractured internal semilunar cartilage. It is to the latter, which are the most difficult to diagnose, that attention will be drawn in this paper.

ANATOMY

The knee-joint is a hinge-joint. While nature was apparently most lax in providing bony reinforcements to the knee, she has been most ingenious in furnishing ligaments strong enough to take up the strains imposed. In front is the anterior or big patellar ligament. This has a ligamentous or tendinous attachment below and a muscular attachment above. Its action as a true ligament, therefore, is not very great. On the inner side is the internal lateral ligament, short, strong, and fan-shaped, with its narrow part downward, and having its deep portion intimately associated with the capsule and the internal semilunar cartilage. The deep fibers, being short, keep the internal semilunar close to the condyles of the femur. On the outer side the external lateral ligament extends from the external tuberosity of the femur to the head of the fibula, splitting the tendon of the biceps in its course. This ligament has two divisions, a weak posterior part and a strong anterior part. It is separated from the capsule of the joint by the popliteus tendon and the bursa found there. The two lateral ligaments are the chief agents in providing against lateral mobility: the internal lateral preventing the knee from bending inward, and the external lateral preventing the knee from bending outward. The rounded ends of the femur are buttressed, as it were, by the internal and external semilunar cartilages, and thus the lateral ligaments are aided in their function (Fig. 381).

The internal semilunar cartilage forms a large segment of a circle and is less movable than the external.   Posteriorly it is firmly attached just in front of the posterior crucial ligament.   Anteriorly it is less firmly attached in front of the anterior crucial ligament.   Internally it has a
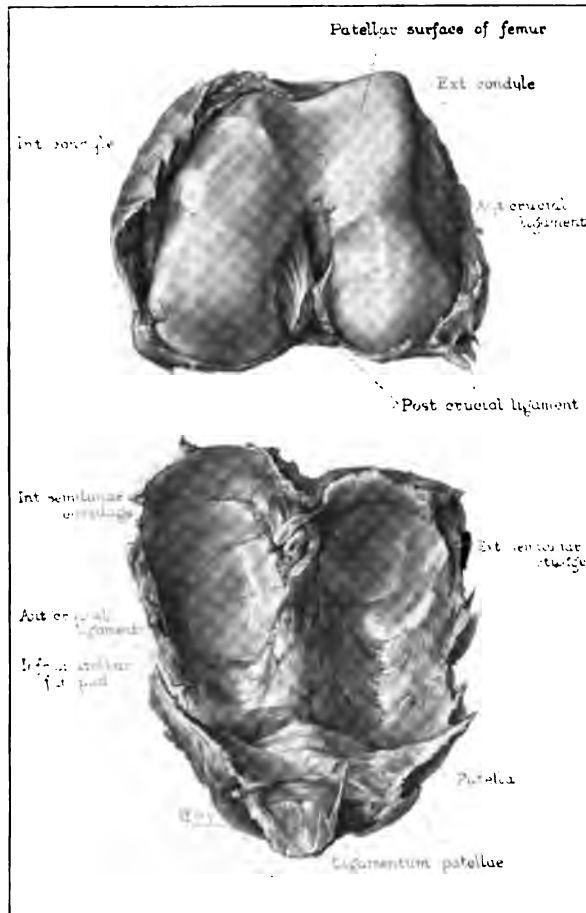
Fig. 581.—Intrinsic structures of the knee-joint.

firm attachment to the lateral ligament and a somewhat weak attachment to the tibia by the coronary ligament.

The external semilunar cartilage forms a smaller segment of a circle. Occasionally it is nearly a complete circle, there being only a small opening against the tibial spine, as in three of the 150 specimens examined by Tenney.[1]   The external semilunar is fixed anteriorly in front of the

tibial spine, and posteriorly to the tibial spine between the tubercles, giving a strong slip to the posterior crucial ligament. The attachments to the external lateral ligaments and the tibia are very weak. The semilunar bodies are spoken of as being cartilaginous. In reality, they are fibrocartilaginous, the thick convex part being largely fibrous tissue, and only the inner concave portion cartilaginous. When this cartilaginous border is injured, small pieces of cartilage may become separated and loose. The fibrous tissue is arranged transversely and longitudinally. The longitudinal fibers may continue anteriorly across to the opposite cartilage, forming the transverse ligament—an insignificant structure. At the convex borders the transverse fibers blend with the capsule. The coronary ligaments are formed by these fibers below and are really only the portion of the capsule between the semilunars and the tibia.

The anterior and posterior crucial ligaments are two very important internal ligaments. The anterior arises from the front of the spine of the tibia near the anterior extremity of the external semilunar cartilage and courses upward, outward, and backward to the inner side of the outer condyle of the femur. The posterior arises from the back of the groove on the posterior side of the top of the tibia and from its outer border, leaving the floor of the groove and the transverse piece of the spine of the tibia free and covered by synovial membrane. Here it is closely connected with the external semilunar cartilage and runs forward, upward, and a little inward to the front of the outer side of the inner condyle of the femur and of the intercondylar notch (Piersol[2]). These ligaments greatly aid in the stability of the joint. Griffiths[3] states that if the internal or external lateral ligament is divided and lateral bending is attempted with the knee extended, the bending allowed is considerable, but if the same is attempted with the knee in the flexed position, no bending is allowed laterally. He concludes, therefore, that inward bending of the knee-joint is prevented in the extended position by the internal lateral ligament, and in the flexed position by the crucials. In flexion the relaxation of the internal lateral ligament allows some rotation. With the knee partially flexed, extension may pull on the anterior or upper part of the internal lateral ligament and thus make some traction directly on the internal semilunar cartilage, there being a few fibers of the quadriceps inserted there. This may explain why the anterior extremity of this cartilage occasionally becomes caught and ripped. Jones[4] says experiments show that hyperextension of the knee is prevented by:

(1) The posterior crucial; (2) the anterior crucial; (3) the internal lateral ligament; (4) the external lateral ligament, and that increased extension is secured as one after another of these is divided. Internal rotation is limited by the internal lateral ligament and the anterior crucial. On external rotation the tibia may slip slightly forward on the femur but is stopped by the anterior crucial. On internal rotation the tibia may slip back a little but is stopped by the posterior crucial.

Mechanical derangements produced by intrinsic causes will be considered under the following heads:

1. Semilunar cartilages.

2. Loose bodies: (a) Of intrinsic origin—chondral and osteochondral bodies; (b) of extrinsic origin—foreign bodies.

3. Synovial fringes.

4. Crucial ligaments.

DERANGEMENTS DUE TO THE SEMILUNAR CARTILAGES

In the English medical literature there are many reports of large series of cases of damage to the semilunar cartilages, but those reported in the American literature are few. This is accounted for largely, I believe, by the fact that the English, as a class, participate much more freely in vigorous pastimes, such as football, Rugby, tennis, hockey, etc., than do Americans. In America the clerk or laboring-man seldom indulges in such pastimes, while in England he participates in them freely.

As stated previously, when the knee-joint is partially flexed a little lateral mobility is permitted. This is due to the fact that the internal lateral ligament is relaxed. As it slacks, however, the crucial ligaments take up their duties, so that when the knee is at right angles, the lateral mobility is checked. From 25 to 90 degrees flexion is an arc of weakness, and it is in this arc that damage to the internal semilunar is most frequently inflicted. According to Jones,[5] the most frequent cause of injury to the internal meniscus is strain thrown on the internal lateral ligament when the tibia is rotated outward while the knee is flexed. In rare instances he has known it to occur when the knee was extended; but, as emphasized by Lane,[6] the internal fibrocartilage is injured in such cases only by great force. In extension, the internal lateral ligament is taut and performing its function, and it must be torn before the internal semilunar fibrocartilage can be displaced. In moderate flexion the crucials are not in a position to maintain stability, and the internal lateral ligament being slightly relaxed, some mobility of the internal

semilunar is allowed. On attempted extension there may be a slight pull on the anterior extremity of the semilunar cartilage by the prolongation of the quadriceps muscle inserted into that part of the capsule, and the cartilage may be caught between the joint surfaces and torn loose or possibly fractured as the leg is straightened. Martin[7] states that damage to the internal semilunar is common among coal-miners who stand with the knees more or less flexed in low seams (4 by 4½ feet) in the mines. A review of our case histories has demonstrated that in the majority of instances the accident occurred with the leg partially flexed, the foot abducted and rotated outward, and force applied which caused the tibia to be rotated outward or the femur to be rotated inward, depending on whether the force was applied above or below the plane of the knee. Locking of the joint is followed by effusion. The pain is often so severe as to make the patient cry out and fall to the ground, grasping the knee with both hands. It is usually most severe at the primary locking, and lessens as the locking becomes more frequent, until by some patients the pain is complained of less than the mechanical obstruction blocking the extension of the leg. The effusion may be considerable following the early locking, but as the lockings become more frequent the joint seems to accustom itself to the condition, and very little if any appreciable amount is noted. In some cases the locking may not be distinct, the patient complaining only that "things do not feel right in the joint." A diagnosis of a damaged fibrocartilage should be made in such cases only after very careful examination and consideration. The roentgenogram is of practically no aid, as in the great majority of instances the fibrocartilaginous body of the misplaced cartilage casts no shadow. Occasionally in persons with a history of lockings extending over many years the irritation inflicted on a pedunculated end of the internal semilunar will so harden it that a faint shadow will show in the roentgenogram between the internal condyle of the femur and the tuberosity of the tibia. In such cases, however, the history is usually so clear that the roentgenogram is not a necessary aid in the diagnosis. Nevertheless, any patient with mechanical derangement of the knee should have the benefit of the roentgenographic examination, for it is impossible to differentiate in many cases between a misplaced or loose internal semilunar or external semilunar cartilage and a loose body. The roentgenogram, therefore, may be considered as of the greatest aid in making a differential diagnosis.

It must be constantly borne in mind that while the most frequent

cause of mechanical derangement of the knee-joint is an injured internal meniscus, other causes also may produce the derangement. In some instances a diagnosis is extremely difficult before operation, and even after the joint is opened the cause is not evident. Surgeons of great experience have acknowledged that occasionally after making a careful search for the condition causing the symptoms complained of they have closed the knee-joint without repairing or removing anything. The removal of the internal semilunar cartilage must be decided from the findings.

According to Lane,[6] periodic derangements of the knee-joint may so lower the vitality of the joint tissues that tuberculosis develops. In his opinion the majority of cases of tuberculosis of the knee-joint have this as their predisposing factor, particularly in persons who have intestinal stasis. In this contention he is supported by Jones,[4] who adds that rheumatoid arthritis also may be so induced. I have seen a few cases of tuberculosis of the knee in which there was a history of mechanical derangements for some years preceding the onset of the tuberculous arthritis. Such a history, however, was the exception rather than the rule.

The treatment of derangement due to the internal semilunar cartilage is either non-operative or operative. It may be taken as a rule that patients should not be operated on who give a history of only one locking. If seen immediately after the accident, reduction should be made at once. Complete extension and the statement of the patient that the joint feels right are evidence that reduction of the displaced cartilage has been effected. If the patient insists that the reduction is not accomplished, it is probable that he is correct. After successful reduction, rest in bed should be insisted on until the effusion has subsided. Flexion of the knee and strain on the internal lateral ligament should be prevented for six weeks. If the damaged cartilage is given the opportunity to unite firmly in its normal position, the chances for a cure are very good. If the primary care has been careless and the fixation period inadequate, the patient very often presents himself with a story of multiple lockings. In these old cases operative interference is necessary, for rest and immobilization at this late time will not insure the fixation of the loose cartilage in its normal position. When operation is necessary for removal of the internal meniscus, the incision of choice is the condylar incision of Jones. It is not necessary to remove the entire cartilage; the anterior three-fifths is usually sufficient. Damage to the

internal lateral ligament may be avoided by limiting the incision and by leaving a thin rim of the fibrocartilage attached to the internal lateral wall of the joint.   This can be done easily by using a tenotomy knife to separate the cartilage, thus avoiding the deep fibers of the internal lateral ligament.

In my series of cases there has been none in which we have found it necessary to remove the external semilunar cartilage.   Jones[4] found it necessary to remove it in twenty-four cases, 7 per cent. of his total. He explains the rarity of damage to this cartilage on the ground that, unlike the internal semilunar, which is securely fastened by its ligaments and cannot slide out of the way of harm, the external is more loosely attached and thus escapes injury.   However, it should be borne in mind when making a diagnosis that the external cartilage is not immune to damage.

LOOSE CHONDRAL AND OSTEOCHONDRAL BODIES

Relatively speaking, loose bodies of cartilaginous or osteocartilaginous consistence are common.   They may be either free or pedunculated. Very often when the body is cast off from one of the articular surfaces a piece of spongy bone comes with it.   As the body wanders about the joint it receives nourishment sufficient to permit the growth of cartilage until it is entirely covered.   Then only by section of the body can the bone be demonstrated (Fig. 382).

The etiology of loose bodies is interesting.   It is generally conceded that a certain definite group have osteo-arthritis or Charcot's disease of the joint as their primary cause.   This group, however, does not directly concern the surgical aspect of the subject, for in such cases the disease is more important than the mechanical difficulties, which are only incidental.   The majority of loose bodies in the knee-joint cannot be explained on these grounds, and it is this majority that are of the greatest interest.   Whitelocke[8] believes that many of them have their origin in the fibrous tags that hang from the synovial membrane.   He states that as the synovial membrane, articular cartilages, and interarticular cartilages are developed from the same primitive embryonic intermediate layer of the axial blastema, these fibrous tags may readily develop into loose bodies of chondral nature.   Koenig,[9] on the other hand, described osteochondritis dissecans as being the cause of loose bodies.   Ridlon[10] and Freiberg[11] have more recently called our attention to this condition and reported cases.   Briefly, it is supposed that the pathology causing

osteochondritis dissecans is a blocking of one of the nutrient end-arteries supplying the joint surfaces, with a consequent desiccation of the localized devitalized area as a free or pedunculated body. Undoubtedly there are such cases. However, it is very difficult to estimate the amount of trauma that may be inflicted on a joint surface by the crushing force exerted on attempted extension of the knee by a curled or crumpled-up semilunar cartilage. Owing to its fibrocartilaginous structure, the semilunar cartilage may itself escape any serious damage and yet severely injure the cartilaginous articular surface. In the majority

Fig. 382.—(116,019.) Anteroposterior view showing loose body at site of origin in internal condyle of the left femur.

of instances no history is to be elicited of a tendency to form loose bodies, but there is a history of direct injury to the internal condyle of the femur by falling on the flexed knee. The injured area may be chipped off at the time, but more often the area of trauma is devitalized and later separates off and becomes a free body. In the greater number of our cases of loose bodies in the knee-joint we were able to demonstrate, either by the roentgen ray or operation, that the bodies originated from the thick ridge of the cartilage placed on the internal condyle of the femur to compensate for the wear caused by the normal action of the joint (Fig. 383).

The symptoms are catching or locking of the joint, accompanied by pain and followed by swelling. Repeated attacks generally tend to decrease the severity of all the symptoms. Very often the patient is able to locate the body and thus establish the diagnosis. The roentgen ray in practically all instances discloses the presence of the body, as the cartilage is usually dense enough to cast a shadow, and in many instances a small flake of bone is attached to the cartilage which further aids in the localization. The continued presence of these bodies in a joint causes continued irritation and is apt to produce arthritis. They should be removed, therefore, but before operation care should be taken to locate them as accurately as possible. After the preparation of the knee has been completed it may be possible to localize the body in the supra-

Fig. 383.—(147,988.) Cross-section of loose body, showing cartilage grown around the bone (× 2½).

patellar pouch or at either side of the ligamentum patellæ. By holding the body between the fingers and infiltrating the skin with local anesthesia, a sharp needle may be pushed through the skin into the body to hold it securely. A small incision down the course of the needle then allows ready removal of the body. More often, however, the body cannot be grasped in this manner, and the patient is given a general anesthetic in order that an incision allowing the best approach to the body may be made. If the body rests in the anterior compartment of the joint and on the inner side, the incision on the inner side of the patella permits the easiest entrance. When a more general exploration is necessary, the splitting of the patella, as described by Corner,[12] allows free inspection of the suprapatellar pouch and the anterior and interarticular areas of the joint. If the body is posterior, the incision described by Brackett and

Osgood[13] through the popliteal space is the most convenient. The mere presence of a loose body in the posterior part of the joint does not demand its removal. Moreover, it should be remembered that occasionally there are sesamoid bones in the hamstrings that are extremely difficult to differentiate. A sesamoid bone may have a concave surface that fits the convex posterior surface of the condyle of the femur, whereas the loose body, because of its wandering, does not have the shape of its location impressed on it, and is often rounded or oblong. Stereoscopic roentgenograms may show whether the body casting the shadow is resting directly on the condylar surface or is located in the intercondylar notch. If in the intercondylar notch, it is presumably a loose body, but if resting on the condyle, it probably is a sesamoid.

FOREIGN BODIES

Foreign bodies cause derangements, but differ from the previous groups mentioned in that they are of extrinsic origin, being introduced accidentally or intentionally from without. In the literature needles are mentioned frequently as a finding. In some instances the patient is not aware of the introduction of the needle. Malingerers occasionally introduce needles in the knee-joint, and the clinical picture is baffling until a roentgenogram is taken. Bullets may enter the joint and be remarkably well tolerated. The presence of a foreign body in practically all instances demands the same operative measures as mentioned for the loose cartilaginous bodies, except that the demand for its removal is even more urgent.

SYNOVIAL FRINGES

Synovial fringes or fat tags occasionally cause mechanical derangements, but the symptoms are usually mild. The condition may be due to mild tuberculosis or to some systemic disease, such as syphilis. These facts, together with the mildness of the symptoms, usually contraindicate operative interference. Such tags, as a rule, have their origin on the alar ligament or the fat pad extending on either side of the patellar ligament. Occasionally during the course of an exploration of the joint I have removed a pedunculated flattened fat tag which looked as though it were being habitually squeezed by the articular surfaces. However, that the fat tag may be the sole cause of joint derangement has not in our cases been shown to my satisfaction. Painter and Erving[14] have

called attention to the possibility that fat tags may cause symptoms and have reported cases.

THE CRUCIAL LIGAMENTS

The results of rupture of one or both of the crucial ligaments are more serious and disabling than those of what are generally understood as mechanical derangements of the knee-joint. Their cause is severe trauma, such as that resulting from the passing of a wagon-wheel over the leg. If, after an injury with the knee in an extended position, the tibia can be pushed forward, the anterior crucial is ruptured. If, with the knee in flexion, the tibia can be pushed backward, the posterior crucial is ruptured. The pain caused by such extensive manipulations usually necessitates an anesthetic. The spines of the tibia may be broken in addition, and occasionally give rise to loose bodies. For ruptured crucial ligaments Corner has advised operative measures. However, when the knee is properly treated from the onset by placing it at rest in slight flexion in a plaster-of-Paris cast and maintaining such fixation for three months, a useful knee results. It is tersely stated by Jones and Smith[15] that "modern practice pays not enough attention to the fact that a ruptured tendon or ligament must not be subjected to strain during the period of healing." Use of an injured knee should be permitted only after careful examination. According to these authors, in a case of rupture of both crucials conservative measures of rest for three to six months promise better results than immediate operation. It is astonishing to what extent, particularly in the young, a knee with relaxed ligaments will regain stability if a suitable brace is provided to prevent strain on the stretched ligaments.

END-RESULTS

The cases forming the basis of this report number 87. They were all under observation in the Mayo Clinic during the interval between January 1, 1910, and January 1, 1916. As many of the patients as possible have been seen or communicated with since their operation, to ascertain the end-result of the treatment accorded them. There were 63 males and 24 females. The youngest was fourteen years of age, and the oldest sixty-seven. The average age was thirty-two years.

The internal semilunar cartilage was judged to be the sole offender and removed in 53 cases. We were able to trace 44 of these patients. Thirty were cured, 9 were relieved, and 5 reported themselves as no

better.   It is probable that a few of the 9 reporting themselves as merely relieved may be considered cured, for in some instances their reasons for stating that they were more or less dissatisfied with the operation were indefinite.   However, as the opportunity to make the examinations and observations necessary to refute their statements was lacking, they have been classified as merely relieved.   The five patients reported as no better were cases in which at operation no definite pathology could be established and the semilunar was removed on insufficient pathologic evidence.   In the majority of these cases it would have been better to have at least deferred operation.   Five patients we were unable to trace.   The internal semilunar cartilages were removed from 8 knees at the same time that loose bodies were removed.   In the majority the loose bodies were the prime cause of the trouble.   All of these patients reported themselves as completely cured.   In 24 instances loose bodies were removed from the knee-joint when they were considered to be the chief offenders.   Sixteen patients reported themselves as cured; 5 were not traced, and 3 were relieved.   The latter 3 cases were those of elderly people who had arthritis associated with the condition.   Undoubtedly much of their present complaint is due to that.

Two cases of rupture of the crucial ligaments were treated conservatively by placing the knee slightly flexed in a plaster-of-Paris cast.   Full function was restored.

To sum up, 56 of the 87 patients operated on for mechanical derangements of the knee due to intrinsic causes were cured; 12 were relieved; 5 reported themselves as no better, and 14 were not traced.

CONCLUSIONS

1. Damaged semilunar cartilages should be accorded the careful treatment by rest and fixation that is given an ordinary fracture of one of the long bones.   Recurrent locking will then be an uncommon sequel.

2. Recurrent locking produced by a loose or fractured semilunar cartilage or loose body demands removal of the meniscus or body under the strictest asepsis.   A judicial exploration of the joint should be made at the same time.

3. The condylar incision is the incision of choice for the removal of the semilunar cartilages.

4. For the removal of loose bodies, the split-patella incision is usually best.

5. A ruptured crucial ligament is better treated conservatively than by operation.

REFERENCES

1. Tenney, B.: "The Anatomy and Surgery of the Internal Derangements of the Knee-joint," Ann. Surg., 1904, xl, 1–34.
2. Piersol, G. A.: Human Anatomy, Ed. 4, Phila., Lippincott, 1913, vol. 1, pp. 404–405.
3. Griffiths, J.: "Observations upon Injuries to the Internal Lateral Ligament and to the Internal Semilunar Cartilage of the Knee-joint," Brit. Med. Jour., 1900, ii, 1171–1175.
4. Jones, R.: "Notes on Derangements of the Knee," Ann. Surg., 1909, l, 969–1001.
5. Jones, R.: "Internal Derangements of the Knee," Lancet, 1914, ii, 297–300.
6. Lane, W. A.: "Some of the Common Injuries of the Knee-joint and Their Consequences," Brit. Med. Jour., 1911, i, 537–539.
7. Martin, A. M.: "Discussion on the Diagnosis and Treatment of Injuries of the Knee-joint Other than Fractures and Dislocations," Brit. Med. Jour., 1913, ii, 1070–1076.
8. Whitelocke, R. H. A.: "Loose Bodies in the Knee, with Special Reference to their Etiology and Growth," Brit. Jour. Surg., 1913–1914, i, 650–664.
9. Koenig, F.: "Ueber freie Körper in den Gelenken," Deutsch. Ztschr. f. Chir., 1888, xxvii, 90.
10. Ridlon, J.: "Osteochondritis Dissecans," Jour. Amer. Med. Assoc., 1913, lxi, 1777–1779.
11. Freiberg, A. H., and Wooley, P. G.: "Osteochondritis Dissecans; Concerning Its Nature and Relation to Formation of Joint Mice," Amer. Jour. Orthop. Surg., 1910, viii, 477–494.
12. Corner, E. M.: "The Surgery of the Knee-joint," Jour. Amer. Med. Assoc., 1914, lxiii, 1069–1075.
13. Brackett, E. G., and Osgood, R. B.: "The Popliteal Incision for the Removal of 'Joint Mice' in the Posterior Capsule of the Knee-Joint," Boston Med. and Surg. Jour., 1911, clxv, 975–976.
14. Painter, C. F., and Erving, W. G.: "Lipoma Arborescens," Boston Med. and Surg. Jour., 1903, cxlviii, 305–309.
15. Jones, R., and Smith, S. A.: "On Rupture of the Crucial Ligaments of the Knee, and on Fractures of the Spine of the Tibia," Brit. Jour. Surg., 1913–14, i, 70–89.

LOOSE BODIES IN THE KNEE-JOINT*

MELVIN S. HENDERSON

Loose bodies occur most frequently in the two large hinge-joints, namely, the knee and the elbow. I shall consider here only those having as their localization the knee-joint. Our lower limbs have to perform double functions: they must have strength to enable us to stand and they must allow locomotion. To permit of free and easy locomotion there are provided articulations complementary one to the other, and these articulations must be of mechanical construction, capable of bearing the body-weight through many angles. The hip-joint is of a ball-and-socket construction, the muscles during locomotion giving aid to the stolidity beside that so adequately provided by the bony structure. The knee-joint is constructed so that the bony prominences aid but little in the stability, and the tendons of the muscles inserted in the immediate vicinity assist to a very slight degree. Consequently nature has been called upon to provide a most efficient ligamentous support for this hinge-joint. When certain ligaments are slackened by a given motion, other ligaments must give support during this motion. In spite of the excellent ligamentous support, there are present in the knee-joint during flexion a little abduction, adduction, and rotation of the leg on the thigh. The maximum of these movements occurs in the arc between an angle of flexion of about 30 degrees and an angle of flexion of 90 degrees. This arc may be spoken of as the arc of weakness. Beyond 90 degrees flexion the stability increases. It is in this arc of weakness that the vast majority of mechanical derangements of the knee are sustained. It must be remembered that the knee-joint is a comparatively superficial joint, and when in flexion direct trauma is very readily inflicted on the condylar surfaces of the femur.

The etiology of loose bodies is perhaps the most interesting side of the subject. The source of these bodies wakened the interest of John

Hunter,[1] and his theory of their production, even if not correct, is interesting. He taught that blood when effused tended to organize and adapt itself to the tissues in which it was effused; thus if the effusion were in the abdomen, a soft tumor resulted, or if in the neighborhood of a bone, a hard one resulted. He believed the organized clot in the knee attached itself to the articular cartilage, assumed its character, and later becoming detached, gave rise to cartilaginous bodies.

The symptoms are so well known and the diagnosis is so simple usually that I shall merely mention them incidentally.

Probably the most logical classifications of loose bodies in the knee-joint are as follows:

1. Fibrinous loose bodies, intrinsic in origin.

2. Bodies composed of .organized connective tissue, e. g., bone and cartilage, intrinsic in origin.

3. Loose foreign bodies, extrinsic in origin.

FIBRINOUS LOOSE BODIES

The fibrinous loose bodies, described as " corpora oryzoidea " by Koenig,[2] are, as the name signifies, composed of fibrin. They consist of concentrically laminated masses of fibrin, and have been variously named, according to their size, "melon-seeds," "rice bodies," "wafer bodies," etc. They are not confined to joints, for they are often seen in bursæ and in tendon-sheaths, and are thought to be pathognomonic of tuberculosis. In joints they frequently occur in large numbers, and here again tuberculosis is usually thought to be their etiologic factor. This same fibrinous material of which they are composed is used to coat foreign bodies, such as needle-points, when the latter are free in the joint. Clinically they produce only slight symptoms. Usually the patient mentions some slight restriction of motion and stiffness. There is almost invariably an accompanying effusion of varying amount, and the bodies may be detected on palpation of the joint. They do not cause the mechanical inconvenience of locking or slipping, such as is produced by loose bodies of the organized connective-tissue group. They are the result of some disease in the synovia, and in tuberculous joints are said to be produced by the extra amount of fibrin thrown out by the cells of the synovial membrane. The following history is typical of this group:

CASE 1 (92,315).—S. H. D., male, aged twenty-nine, examined September 18, 1913. For two years, following an indefinite sprain while

working exposed to cold and wet, there had gradually developed a soreness and aching in the right knee. The extremes of motion were restricted, and all symptoms were worse on change of weather. Palpation of the joint revealed the presence of fluid and the semi-crepitant "feel" of rice bodies could be elicited. The roentgenogram showed merely synovial thickening. On September 28, 1913, the joint was explored and about four ounces of straw-colored fluid was aspirated and multiple rice bodies were removed. The joint was thoroughly irrigated with saline solution to remove as many of the rice bodies as possible and was then injected according to the method of Brackett, except that 2 per cent. formalin and glycerin was used instead of an iodoform suspension. The aspirated fluid was injected intraperitoneally in a guinea-pig with negative result. Two and a half years later the man wrote that the knee was much improved, though motion was still somewhat restricted. He had walked recently 15 miles in one day with no discomfort.

BODIES COMPOSED OF ORGANIZED CONNECTIVE TISSUE

These bodies form a large and interesting group. Their histologic structure is of interest, for they are usually spoken of as being cartilaginous. While cartilage is the main part of the body, yet frequently on section there will be seen a flake of bone. In my experience the majority of these bodies have arisen from the internal condylar surface of

Fig 384.—(147,988.) Cross-section of loose body, showing how cartilage has grown around the bone (× 2½).

the femur. They come from the ridge of thick cartilage on the internal· condyle provided to compensate for the wear caused by the hinge-like action of the joint. When a large piece of cartilage is chipped out from this area, there is usually a small piece of the spongy bone from the epiphysis with it. The cavity left in the condylar surface, if small, fills in again with cartilage, but if large, a scar is left which can be detected in the roentgenogram and at operation. The loose body wanders about the joint, and in some instances receives sufficient nourishment from the joint-fluid to increase its size; it becomes rounded until the bony part of the body is completely surrounded with cartilage (Fig. 384). The bodies may be further subdivided into: (a) Those having as their etiologic

factor some disease, such as osteoarthritis or Charcot's disease, and (b) those due to injury. The loose bodies due to disease and those due to injury are inseparable in certain cases; an osteophytic growth due to osteoarthritis may readily be loosened by joint trauma, direct or indirect, and become a loose body.

It has long been recognized that osteoarthritis is the etiologic factor in the production of a considerable number of loose bodies. Loose bodies due to the disease are usually multiple in the individual joint. The inflammation due to the disease acts on the articular extremity of the bone and also involves the contiguous structures of the joint. There result an erosion and fibrillation of the cartilages and eburnation of the bones, with osteophytic growths, which break off and wander about the joint as loose bodies. By their wandering they produce further irritation, and locking of the joint is of frequent occurrence; the effusion is increased, with consequent stretching of the synovial sac and its incorporated ligaments, thereby making the joint less stable. Other conditions being equal, the removal of these bodies when producing such symptoms is essential for the comfort and safety of the patient. The following case is cited as illustrative of this group:

CASE 2 (108,373).—Mrs. J. R. H., aged sixty, examined March 17, 1914. History of rheumatism for twenty years, involving all joints and with slow changes in finger-joints. Two and a half years before, on getting up from a chair, she had a sudden sharp pain in the right knee, so severe that she cried out. Swelling followed. One month later a definite locking occurred and this was repeated many times. The roentgenogram showed, in the hands and knee, typical osteoarthritic changes, with a body lying in the suprapatellar pouch. Apparently this loose piece of cartilage and bone originated in an osteophytic growth which had broken off and later increased in size. June 30, 1914, the body, one and one-half by three-fourths by one-fourth inches, was removed through an incision just above and to the outer side of the knee. Relief of the locking followed, but stiffness and soreness, due to the arthritic condition, persist to date.

Occasionally associated with hypertrophic arthritis there is a loose body in the knee-joint that may be looked on as the cause rather than the result of the arthritis. The following case is an example:

CASE 3 (135,273).—S. A. A., male, aged fifty-two, examined July 8, 1915. Twenty-four years previously this patient sustained a severe trauma to the inner side of the right knee. One month after the accident locking occurred, and would recur many times a day. For ten years this frequent

locking was present, but disappeared when the body found a favorable resting place above the patella, "out of the joint." Up to one year before our examination he had no further trouble, though the body was always to be felt in the suprapatellar pouch. Without any direct trauma, though he had been subjected to extra exertion, the body slipped "into the joint" and the locking recurred. When able to keep the body above or to the inside of the patella, he was free from trouble. Physical examination did not disclose affections of any other joint. The roentgenogram of the knee showed hypertrophic arthritis, a calcified body posteriorly, and a larger one in the suprapatellar pouch (Fig. 385). On July 16, 1915, under local anesthesia a large body, one and one-half inches in circumference and about one-fourth inch thick, was removed from the suprapatellar pouch. The edges were rough and irregular. The patient's recovery was uneventful and complete.

Occasionally loose bodies are found in Charcot joints. It is necessary to emphasize that a Charcot joint is essentially a neuropathic joint, and only under unusual circumstances would operation be warranted. All too frequently these patients have been subjected to operation for the removal of a loose body when the body was entirely a secondary consideration.

Fig. 385.—(135,273.) Loose body in suprapatellar pouch and a smaller one in the posterior compartment.

The patient presenting himself with loose bodies in the knee-joint, who admits a syphilitic infection years before, should put us on our guard. As a rule, the patient with a Charcot joint tells us that the affected joint gradually becomes a little unstable and some slight soreness develops. A history of darting pains in the lower limbs can frequently be elicited, and a careful neurologic examination should be insisted on. Sensory disturbances, even though slight, are very important in the diagnosis. These findings, taken into consideration with the fact that we are dealing with a joint that is hypermobile and at the same time practically painless, establish the diagnosis of a Charcot joint. Such loose bodies are, then, only secondary considerations.

CASE 4 (140,939).—H. G. C., male, aged forty-seven, examined September 10, 1913. He gave a six-year history of weakness in the right knee, following a fall from a ladder. The knee was not subjected to a roentgen examination. On passive motion it was easily hyperextended, and there was lateral mobility in all positions. On walking there was marked outward bowing. There was only slight pain with soreness on excessive use. The neurologic examination was negative. No venereal history was admitted, but the Wassermann reaction was strongly positive. The roentgenogram showed multiple loose bodies and destructive arthritis. A brace was provided to give stability to the knee; the removal of the loose bodies was not advised.

A hypertrophied fat tag may cause mechanical inconvenience in the knee-joint. It is rather rare, though Painter and Erving[3] lay stress on the fact that it does at times cause restriction of motion and pain. I have rarely seen such a case. In our cases the fat tags have been secondary to chronic diseases, such as tuberculosis and syphilis. In none of this series have there been operations for the relief of such a condition per se.

Occasionally, in a joint with one or more large loose bodies, a rather interesting condition is seen. The synovia is thickened, congested, and has little papillary outgrowths. Various stages in the growth of these papillary bodies can be seen; some are merely the pouching of a localized piece of synovial membrane, while others are pedunculated, though soft and of the consistence of the synovia. Others are fibrous or cartilaginous on the tips, and the pedunculation being more marked, only a slight trauma is necessary to detach one of them and produce a free fibrous or cartilaginous small body in the joint. These bodies may remain small, or, acquiring their nutrition from the joint-fluid, increase in size. Whitelocke[4] is of the opinion that these fibrous tags readily become cartilaginous, and are the loose cartilaginous bodies that so frequently produce symptoms. His theory is opposed to that of Koenig, but he lays particular stress on this point and argues it on embryologic grounds. He states that the development of fibrous tissue into cartilage is due to the fact that the early development of the synovial membrane, articular and interarticular cartilages of the knee-joint are all from the same primitive embryonic intermediate layer of the axial blastema. I can only say that I have but in one instance seen anything approaching this condition. The illustrative history of this patient is as follows:

CASE 5 (131,188).—T. K., male, aged forty, examined May 7, 1915. Twenty-three years before, following a fall on the ice, the knee became swollen and painful. Recovery was complete, and for seventeen years

the man had absolutely no discomfort in his knee; then it began to swell
a little after exertion. Various remedies, such as massage, blistering,
and electricity were tried, with no relief, but he managed to carry on his
work on a farm. The year preceding our examination the swelling and
pain finally necessitated the abandonment of his work. No history of
venereal infection could be elicited, and repeated Wassermann tests
were negative. The roentgenogram showed multiple loose bodies in the
knee-joint, the condylar outline rather hazy beneath the patella, and
what appeared to be degenerative changes in the lower end of the femur
(Fig. 386). The joint was explored by a median incision, splitting the
patella. Multiple loose cartilaginous bodies were removed, the largest

being one inch by one-
fourth inch. The smaller
ones appeared to have their
origin in the synovial mem-
brane. Little pouches of
synovial membrane, vary-
ing in size from a pinhead
to a small pea, protruded
into the joint. Some of
these were white and fibrous
on their tips, others were
becoming   cartilaginous
and had small pedicles. An
exostosis, about one-half
inch in diameter, was re-
moved from the external
condyle. The exostosis evi-
dently originated in the cav-
ity left by the large body.
Through a separate inci-
sion on the inner side of the

Fig. 386.—(131,188.) (a) Multiple loose bodies; (b) exostosis, and
(c) degenerative changes in the lower end of the femur.

knee the degenerative condition of the lower end of the femur was explored.
It was not vascular; a cartilaginous fibrous tissue was obtained, and on
microscopic examination, was pronounced benign. No relief followed the
operation. The patient returned four months later, with his knee much
larger and motion greatly restricted. The roentgenogram showed that
the apparent degeneration in the lower end of the femur was much more
advanced. Amputation was done at the upper third of the thigh.
Pathologic report: Chondrosarcoma. The patient's general health de-
clined, and two months later the roentgenogram showed metastases in
the lungs.

Loose Bodies Caused by Injury

The loose bodies caused by injury, either direct or indirect, are usually
found in persons in the active period of life, who are exposed to the

traumas incidental to athletics and open-air vocations. The production of loose bodies is often attended by so little trauma that we must look for some explanation other than trauma. Koenig[7] in 1887 first described osteochondritis dissecans. More recently Freiberg[5] and Ridlon[6] have called our attention to this condition. Such cases as these authorities have described account to a large extent for the group of loose bodies in which there are inconsequential histories of trauma. It is thought better to group these under the head of injury rather than disease, though there are arguments for their inclusion under the latter. A comparatively slight trauma might produce a loose body in a

Fig. 387.—(148,865.) Flattened area on the internal condyle, from which the loose body arose. The loose body was to the inner side of the patella.

person affected with osteochondritis dissecans, whereas the same trauma in a normal person would not be productive of trouble. Osteochondritis dissecans is probably not so exceedingly rare as was at first believed, and the theory of Koenig accounts, more or less satisfactorily, for the production of these bodies, but leaves us in the dark as to why this pathologic process should occur. His theory is based on the fact that arteries supplying the contiguous joint-surfaces of the femur and tibia are end arteries, and that

Fig. 388.—(148,865.) Loose body, left knee suprapatellar pouch.

a blockage or failure to act on the part of one of these arterioles shuts off the nourishment to a certain localized area. This devitalized area then becomes separated and may, by a direct injury, or even the normal action of the joint, be cast off as a free body, or the fragment may hang by a fibrous pedicle. We occasionally see persons who have had "joint mice" removed from both knees. The following case history is illustrative of osteochondritis dissecans in both knees:

CASE 6 (148,865).—A. Q. A., male, aged thirty-four, examined December 30, 1915. One year before this man's left knee locked when swinging himself around a newel-post on going down-stairs. A few weeks later a loose cartilaginous body was removed from the suprapatellar pouch, with relief of all symptoms. Two weeks previous to our examination he twisted his right knee slightly in getting off a· train; locking occurred, followed by pain and swelling, necessitating rest in bed for a few days. A roentgenogram (Fig. 387) of the right knee showed an eroded area on the internal condyle and a loose body. The loose body (osteocartilaginous) was removed by splitting the patella. While convalescing, the patient located a loose body in the left knee. This was removed under local anesthesia. A roentgenogram (Fig. 388) of the suprapatellar pouch showed a loose body, evidently having its origin from the internal condyle. There was no history of trauma, direct or indirect, to the left knee, since the first body was removed from it the year before. If produced at the same time as the first body, it must have been resting quietly in some pouch, for there were no symptoms.

Occasionally a person apparently in perfect health may, on strenuous, yet not unusual, exertion for that person, produce a loose body in the knee-joint. There is in this type no history of direct trauma, and any injury to the articular cartilages must have been produced by intrinsic trauma. We can explain the production of damage to the semilunar cartilages by the normal, and at times hazardous, mobility allowed these cartilages and the hinge-like action of the joint on them; but the smooth surface of the articular cartilage should not produce on the other articular surface an injury severe enough to devitalize an area and to cause its desiccation. It is possible that the semilunar cartilages may themselves have withstood the applied force, due to their fibrocartilaginous structure, but this same force applied through them may have inflicted upon the more brittle osteocartilaginous surface an injury sufficient to chip a piece off or to devitalize it so that, in the course of a few weeks, the bruised area may be thrown off as a loose body. The following case would fall under osteochondritis dissecans, and is an example of the condition in a single joint.

Fig. 389.—(112,029.) Loose body, intercondylar space.

Fig. 390.—(112,029.) Area on internal condyle, the origin of the loose body.

CASE 7 (112,029).—I. B. H., male, aged twenty-three, examined August 3, 1914. This man complained of his right knee; inability to completely extend it. There was some swelling. The onset occurred one month before, on arising from sitting "tailor fashion." He felt a slight pain, especially in the posterior part of the joint, and could not completely extend the leg. From that time on he had a feeling of "things not being right" in the joint. There was at no time typical locking. The roentgenogram (Fig. 389) showed a loose body in the intercondylar area. It was apparently between the condyles, and seemed to have come from a spot on the internal condyle of the femur. On exploring the joint the body was found lying between the condyles of the femur. The area from which it came on the internal condyle (Fig. 390) was plainly evident. The patient's recovery is complete.

The story of direct trauma may be so definite that we cannot doubt that the loose body originated in the devitalized area caused by the injury. Falling on the bended knees and striking on a hard object is a common cause of direct trauma inflicted on the cartilaginous surface of the femoral condyles. Loose bodies have been reported arising from the tibial articular surface, but I have as yet to see this origin.

Fig. 391.—(142,135.) (a) Two shadows of loose bodies, intercondylar space. (b) Area on internal condyle disclosing the source.

CASE 8 (142,135).—W. D. H., male, aged thirty-eight, examined September 27, 1915. Disability in left knee. Four months previously the man jumped over a fence and, swinging to the left as he fell, struck on his left knee in the flexed position. On getting up he walked with great difficulty, and the next day took to his bed. The leg was flexed to a right angle, but in ten days, under extension, the knee gradually straightened. Swelling was marked. Extension was maintained for nine weeks, and casts within two days of the time of our examination. He had a feeling as though there was something out of place in the joint. He was able to completely extend and flex to a right angle. Swelling was still present. The roentgenogram (Fig. 391) showed loose bodies in the joint, probably

two, in the intercondylar space. They were quite dense, and a flattened area was noted on the internal condylar surface, apparently the source of the loose bodies. On October 13, 1915, the patella was split longitudinally and two loose bodies were found, one two centimeters in diameter in the suprapatellar pouch, and another about three centimeters in diameter between the condyles. The internal condyle was flattened over an area about the size of the large, loose body, showing clearly the source of this body.

The following history shows how long some patients endure the presence of these bodies, with no harm to the joint.

CASE 9 (128,776).—C. A. E., male, aged twenty-nine, examined April 26, 1915. Twelve years ago he fell, striking his flexed left knee on the edge of a wagon box. No very appreciable swelling followed, and he was able to go about his duties. Soon afterward locking occurred and continued to date. The man estimated that there had been more than 100 lockings, appreciable swelling seldom being a sequela. He occasionally felt a loose body, to the inner side of the patella or above it. The roentgenogram (Fig. 392) showed a loose body just posterior to the patella. On April 29, 1915, under local anesthesia, the cartilaginous body was removed from beneath the patella. The origin could not be determined, and no hypertrophic arthritis was evident in spite of the long residence of the loose body in the knee-joint.

Fig. 392.—(128,776.) Loose body with a twelve-year history of locking.

Damage to one of the fibrocartilaginous menisci in the knee may be productive of a loose body, and occasionally even a free body. The structure of these menisci is such that the inner or concave edge is thinned out and is practically pure cartilage. Any pinching of the cartilaginous rim might readily cause a piece to be thrown off as a free body, to float at will about the joint. A continuance of force applied to the semilunar cartilage, after it has been ripped from its attachment to the

lateral wall of the joint sac, could very readily, and often does, produce a fracture with destruction of the cartilaginous substance at the line of fracture. This cartilage in the semilunars is probably never replaced by true cartilage, but only by fibrous tissue. This would allow the portion of the meniscus which is torn from its attachment to the head of the tibia and lateral ligaments to hang as a loose, pedunculated body. Its mobility would vary according to the length of the pedicle.

CASE 10 (129,764).—J. C., male, aged thirty-six, examined April 28, 1915. This man came to the Clinic on account of frequent locking of the left knee for the past eighteen months. He had been thrown on a pile of stones from his wagon by a runaway team of oxen. Locking occurred at once, and great swelling followed. He had practically full motion at the time of our examination, but a little swelling was present, the last locking having occurred six days before. The roentgenogram was negative. Exploration of the joint by the condylar incision showed a partially fractured, loose internal semilunar cartilage; also a small free piece of cartilage which had been torn off the inner margin of the internal semilunar cartilage. Recovery uneventful.

CASE 11 (151,787).—H. G. A., male, aged twenty-two, examined February 9, 1916. Six years before, he injured his knee playing football. Frequent catches and lockings to date. At times he felt a small movable body on inner side of knee. Locking occurred during examination and the body could be felt. The roentgenogram was negative. On February 11, 1916, the joint was opened and a fractured internal semilunar cartilage was disclosed. The anterior half was greatly atrophied and hung into the joint as a fibrocartilaginous band—a distinct pedunculated loose body.

LOOSE FOREIGN BODIES

Loose bodies, extrinsic in origin, are occasionally introduced, either accidentally or intentionally, into the knee-joint. They may, and usually do, produce infection, with the disastrous sequelæ so well illustrated by the reports that are emanating from the hospitals caring for the wounded of the present European conflict. In striking contrast are the cases we see in civil practice, in which the foreign bodies are occasionally remarkably well tolerated by the joint. Their presence is, of course, sufficient indication for their removal, unless very unusual circumstances contraindicate the procedure.

CASE 12 (77,702).—R. K., male, aged ten, examined December 26, 1912. Five weeks previously the boy was accidentally shot on the external surface of the right knee with a No. 22 bullet. Marked swelling fol-

lowed, but there were no constitutional symptoms. Many times the boy was able to locate the bullet definitely on the inner side of the knee, but it always quickly disappeared on slight manipulation. The removal of the bullet had been attempted at his home, but it could not be located, and the search was abandoned. The roentgenogram (Fig. 393) showed the bullet in the posterior compartment of the knee, but later it moved, until, at the time of our exploration, it was in the middle of the joint. On December 28, 1912, the joint was opened and the bullet, coated with fibrin, removed. Recovery uneventful.

Fig. 393.—(77,702.) Bullet in posterior compartment. It later moved to the center of the joint.

CASE 13 (55,693).—L. G., female, aged ten, examined July 10, 1911. Six days previously she knelt on a rug, and the head of a needle, with about one inch of the shaft, penetrated the knee-joint. No constitutional symptoms or marked local symptoms followed. The roentgenogram showed the needle lying, apparently, on the internal tuberosity of the tibia. Movements of the right knee were painful, the knee being held stiff. There was a little swelling. On July 15 the knee-joint was opened by following the scar of entry of the needle. The needle, coated with fibrin, was easily removed.

Fig. 394.—(146,719.) Needle embedded in internal condylar cartilage.

CASE 14 (146,719).—G. S., male, aged eight, examined November 29,

1915.   Three weeks previously the boy drew a piece of a needle out of the front and inner side of his left knee.   He did not remember the needle entering the knee, and the first thing he noticed was the piece of needle sticking out through the skin.   The knee gradually swelled, became sore, and ached, particularly at night.   There was some slight limitation of motion, and the boy limped.   The roentgenogram (Fig. 394) showed a piece of the needle evidently embedded in the inner condyle, about the level of the lower end of the patella.   On December 3, 1915, the joint was opened by an internal incision.   A little flake of fibrin was plugging the hole of entry in the cartilaginous surface of the internal condyle. It was necessary to chisel off a little of the cartilage before the piece of needle could be removed.   Recovery was uneventful; the knee is normal.

TECHNIC

As in all joint surgery, the most rigid asepsis is essential, and must be available before these bodies are molested.   The occasional removal under local anesthesia, in the consultant's office or in the home, even though successful, is to be condemned.   If the body can be located and held in place by the sterile gloved hand or by a transfixing needle, the removal can be quickly accomplished under local anesthesia.   Unfortunately, this cannot always be done, and then a general anesthetic should be given, and the incision used which offers the easiest approach to the body.   This may be made laterally on either side or by splitting the patella.   The latter incision is not a suitable one for routine knee surgery, for through it the removal of a semilunar cartilage is difficult. The condylar incision is better for removal of the meniscus.   Bodies intrinsic in origin of any size, in the posterior part of the joint, rarely demand removal, but when necessary the incision described by Brackett and Osgood[7] is the best.   Bodies extrinsic in origin in this situation had better be removed, even if too large to find their way into the anterior compartment.   If the body eludes the surgeon, although an embarrassing occurrence, a second attempt, at a more opportune time, is better than a too prolonged search necessitating considerable manipulation and trauma, thereby increasing the risk of infection.   The fingers should not be introduced into the joint for exploration.   The following history demonstrates how it is occasionally necessary to subject the patient to two operations.

CASE 15 (97,040).—F. M. K., male, aged twenty-eight, examined December 12, 1913.   There was a history of typical locking for twenty years, following direct trauma to the inner side of the right knee.   Effu-

sion never completely subsided. The roentgenograms showed two loose bodies in the joint. Operation, December 18, 1913. An incision was made and a loose cartilaginous body a little more than 2 centimeters in diameter was removed. The other body could not be located, and it was thought probable that it had gone to the posterior compartment of the joint. The effusion and locking persisted, and a roentgenogram two months later showed the second body in the suprapatellar pouch. April 30, 1914, the joint was again opened through the old incision, and

Fig. 395.—(97,040.) (a) Loose body removed at first operation. (b) Two months after removal of first body this loose body migrated from the posterior compartment and caused symptoms necessitating its removal from the suprapatellar pouch.

a piece of cartilage about 2½ centimeters was removed. The internal semilunar was normal, and was not removed. Recovery complete and permanent.

In cases of disability, the fact that but one loose body is found should not preclude a judicial exploration of the joint. A very careful study of the roentgenogram is imperative before operating, and the plate should be at hand during the operation. A faint shadow noticed at some spot away from the apparently main offender should be, if practicable, carefully investigated when the joint is open.

CONCLUSIONS

1. Fibrinous loose bodies are due to some disease condition of the joint, and do not cause mechanical derangements.

2. Organized connective-tissue loose bodies produce mechanical derangements.

3. Loose bodies may have as their primary cause some condition, such as osteoarthritis or Charcot's disease, but the secondary cause is direct or indirect trauma.

4. Osteochondritis dissecans is a group standing more or less distinctly out from the rest. The bodies seem to be produced by very slight indirect trauma. It is, however, difficult to estimate the degree of indirect trauma, and for that reason they had better be considered as due to trauma rather than to an actual disease.

5. Trauma, direct or indirect, is essential to the production of a loose body.

6. Surgery offers the only permanent relief, and the general condition of the patient being satisfactory, the bodies should be removed.

REFERENCES

1. Hunter, J.: Quoted by Whitelocke, loc. cit.
2. Koenig, F.: "Ueber freie Körper in den Gelenken," Deutsch. Ztsch. f. Chir., 1888, xxvii, 90.
3. Painter, C. F., and Erving, W. G.: "Lipoma Arborescens," Boston Med. and Surg. Jour., 1903, cxlviii, 305–309.
4. Whitelocke, R. H. A.: "Loose Bodies in the Knee with Special Reference to Their Etiology and Growth," Brit. Jour. Surg., 1913–1914, i, 650–664.
5. Freiberg, A. H., and Wooley, P. G.: "Osteochondritis Dissecans; Its Nature and Relation to Formation of Joint Mice," Amer. Jour. Orthop. Surg., 1910, viii, 477–494.
6. Ridlon, J.: "Osteochondritis Dissecans," Jour. Amer. Med. Assoc., 1913, lxi, 1777–1780.
7. Brackett, E. G., and Osgood, R. B.: "The Popliteal Incision for the Removal of 'Joint Mice' in the Posterior Capsule of the Knee-joint," Boston Med. and Surg. Jour., 1911, clxv, 975–976.

THE INTRAPERITONEAL INOCULATION OF ANIMALS; ITS DIAGNOSTIC VALUE IN ORTHOPEDIC SURGERY *

MELVIN S. HENDERSON

The diagnosis of tuberculosis places upon the surgeon considerable responsibility. Particularly does this apply to the orthopedic surgeon, the treatment of a tuberculous condition requiring in most instances prolonged supervision. Therefore any procedure that makes possible an exact diagnosis should be resorted to.

For the last three years it has been our custom in the orthopedic division of the Mayo Clinic to use as an aid in the diagnosis of suspected tuberculous cases animal inoculation tests. This procedure is an old one, and has been generally used for years, but we believe not with the frequency in orthopedic surgery that it should have been. It is with the idea of presenting the practicability and the clinical value of the test that this paper is offered.

We have as a basis for this communication records to January 1, 1916, of 143 patients who have furnished material for the test. A considerably larger number of tests have been carried out, for in some instances material was obtained two or three times from the same patient. The source of material was as follows:

1. The knee-joint, 80.
2. Abscesses, such as psoas, lumbar, etc., 23.
3. The ankle-joint, 7.
4. The elbow, 5.
5. The wrist, 3.

The balance constitutes a miscellaneous group of hip-joints, shoulder-joints, osteomyelitis, dactylitis, tenosynovitis, etc. In 40 instances tuberculosis was demonstrated at necropsies of the guinea-pigs used and in 103 negative results were obtained.

THE KNEE-JOINT

Material for inoculation was obtained from the knee-joint in 80 instances. The negative reports numbered 58 and the positive 22. Of the 22 positive results, 7 may be put down as merely corroboratory of evident clinical conditions. Fifteen of these 22 positive results were more than corroboratory; a few were of exceeding interest and of distinct diagnostic value. Three cases are herewith cited:

CASE 1 (103,272).—P. V., male, aged ten months. Examination March 28, 1914. Two months before the child became fretful and cried if his left leg was moved. About the time of the onset of the knee symptoms he had a cough, and bronchopneumonia was suspected by the attending physician. The left knee gradually swelled. At the time of our examination the lungs were negative. Above the patella was a marked swelling, which was red, fluctuating, and appeared about to rupture. The diagnosis rested between tuberculosis and pneumococcus infection following pneumonia. The appearance of the knee and the age of the patient argued against a tuberculous joint. The roentgen ray did not show involvement of bone. The suprapatellar pouch was opened and one-half teacup of débris and pus evacuated from the joint. The wound healed by first intention. A saline emulsion of this material was injected intraperitoneally in a guinea-pig and gave a positive test. The baby was placed on a frame with the leg tied down in extension for one year. One and a half years later, the time of the last report, the knee was, to all appearances, perfectly well, though the child has used it very little as yet.

CASE 2 (106,405).—Mrs. C. G. A. Examination May 14, 1914. Two years before this patient had had a sudden onset of pain followed by swelling in her right knee. She was subject to occasional sore throat. The trouble in the knee-joint was steady though mild with exacerbations; some swelling persisted; occasional pains were also complained of in the right hip. The diagnosis rested between an ordinary infectious condition, the focus presumed to be tonsillar, and tuberculosis. The tonsils were removed and fluid aspirated from the right knee for inoculation. No relief followed removal of the tonsils. The guinea-pig test of the knee fluid was positive. Six months later the knee symptoms increasing under rest, the joint was resected. The pathologist's report on this specimen was tuberculosis.

CASE 3 (115,698).—F. S., female, aged twenty. Examination September 22, 1914. The year before her work for a time necessitated prolonged kneeling. Following this a little stiffness and swelling of the left knee occurred. At the time of onset she had an infection on the second left

toe which rapidly healed. It was thought that the knee affection might be secondary to this. The complaint persisted, and during the next year three inoculation tests were carried out. The last one was positive.

It has been stated by some authorities, notably Robert Jones[1] and Sir Arbuthnot Lane,[2] that internal derangement of the knee-joint may be an etiologic factor in the production of tuberculosis of that joint. We have noted that occasionally a patient with a tuberculous knee will give a past history suggestive of some mechanical derangement of the joint. In some it has been a quite definite record of locking, relieved by manipulation; in others, it was merely a catching. This in our experience has been, by no means, the rule. The following two cases are of interest as bearing directly on this phase of the etiology:

CASE 4 (81,603).—B. B., male, aged twenty-two. Examination March 18, 1913. This man had sustained a severe trauma to the right knee five months before. Roentgen ray showed loose bodies in the joint. Effusion persisted in spite of rest. Aspiration was done and five ounces of clear serous fluid were withdrawn. Two cubic centimeters were injected into a guinea-pig. Three weeks later three good-sized loose bodies were removed from the knee-joint. Nothing abnormal beside the loose bodies was noted at the operation except that the infrapatellar pad was markedly congested. The patient's convalescence was normal. Two months later the guinea-pig died and necropsy showed tuberculosis. A recent communication from the patient reports full motion of the knee. His only complaint is that this knee tires a little easier than the other.

CASE 5 (136,312).—P. A., male, aged fifty-two. Examination July 20, 1915. Typical history of loose internal semilunar cartilage following trauma in 1911. Operation for removal of the meniscus performed at his home the same year. Except for an occasional slight stiffness there was no complaint for four years. Four months before our examination stiffness, limitation of motion, swelling, and a little aching developed gradually. Injection of the aspirated fluid intraperitoneally gave positive results.

Of the negative results, more will be said later, but one case is cited here:

CASE 6 (110,917).—F., male, aged fifty. Examination July 22, 1914. Swelling of the right knee was first noted one year before. There were present at the time of our examination a little stiffness and slight swelling and pain on extreme flexion. Roentgen ray showed a mild hypertrophic arthritis. The symptoms persisting in spite of treatment, the patient consulted another surgeon, who made a diagnosis of probable

tuberculosis and gave a poor prognosis.   Four negative tests of the fluid corroborated our diagnosis of a non-tuberculous condition.   The subsequent course has further substantiated this conclusion.

ABSCESS GROUP

This group may be reviewed in a very few words.   The clinical findings are usually sufficient to differentiate a tuberculous abscess from one due to mixed infection.   There are 23 patients in this group.   Negative results were reported in many cases that were clinically clearly tuberculous—undoubtedly repeated injections with non-antiforminized material would have resulted in positive tests.   We had in all five positive tests, none of which had sufficient bearing on the diagnosis nor were of sufficient interest to cause us to dwell longer on this group.

THE ANKLE-JOINT

In this group there were 7 patients.   Three gave negative results; clinically they seemed to be tuberculous.   In 2 of these the material was obtained by curettage of the ankle and digested with antiformin. Only one test was made in the remaining negative case, the patient having great destruction of the joint, necessitating amputation.   The remaining four patients gave positive returns.   In one of these the test was made with material obtained from an astragalus, which was removed; in three, fluid was aspirated from the ankle-joint and injected. Three of the positive histories are here reported.

CASE 7 (78,255).—F. G., male, aged fifty-four.   Examination January 8, 1913.   Six months before a box had dropped on this man's left foot, causing intense pain for a few moments.   There was no immediate disability, but one month later pain, rather general in character, began in the foot.   He became lame, and disability gradually increased, necessitating crutches.   There was a small localized fluctuating mass on the outer side of the foot in the region of the ankle-joint.   Roentgen ray showed merely marked osteoporosis of the bones of the foot and ankle. The fluid was aspirated and injected intraperitoneally, giving a positive result.

CASE 8 (144,659).—J. C., male, aged two and one-half years.   Examination October 30, 1915.   Seven months before the child began to limp and complained of pain in his right ankle.   Roentgen ray showed a destructive process in the right astragalus.   Fluctuation was present over the front of the ankle-joint.   Aspiration of the joint furnished fluid for inoculation, and a positive report was returned.

CASE 9 (146,444).—A. A., male, aged forty-three.   Examination No-

vember 24, 1915. For four months pain and swelling had gradually increased in the left ankle and foot. Lateral strain on the ankle caused severe pain. The roentgenogram showed destructive arthritis. Fluid was aspirated from the ankle and subjected to the test, giving a positive result.

The elbow-joint, wrist-joint, and fingers make up a group of nine cases. With the exception of a patient presenting himself with a tumor on the finger, the results were of no particular significance, the positive test in three cases being merely corroboratory. The history of the patient with the nodule on the finger was interesting.

CASE 10 (82,427).—Male, aged thirty-nine. Examination April 4, 1913. For ten years there had been present a small movable nodule on the outer aspect of the proximal phalangeal joint of the forefinger. No change had taken place in this for nine years, but during the last year it had increased in size, with accompanying tenderness. The diagnosis rested between malignancy and tuberculosis. The presence of pus suggested tuberculosis, but this might easily have been accounted for by the fact that just previous to our examination the swelling had been twice lanced. Microscopic examination of the tissue removed showed merely inflammatory changes. An emulsion of some of the tissue injected intraperitoneally caused tuberculosis.

The balance, 24 in all, were patients suffering from tuberculous shoulders, suspected hip disease, osteomyelitis, periostitis, etc.—5 of these gave positive tests. We cannot here profitably discuss them. They will be included in the general discussion of the series.

DISCUSSION

These tests were made in the bacteriologic laboratory of the Mayo Clinic by Dr. H. A. Sanford. He has kindly furnished me the following regarding the actual technic:

Technic of Animal Inoculation.—"In all of this work we have followed only the old and well-known methods described in all text-books. It may be of interest, nevertheless, to describe briefly the procedures necessary for diagnosis of tuberculous infections by means of animal inoculation. No elaborate equipment is necessary, and any one who has a place to keep a few animals can successfully carry out these tests.

"We have injected clear, straw-colored joint fluids, purulent exudates and discharges, and emulsified tissue. This last has consisted of cartilage, necrotic bone, etc. At one time we would mince the tissue

with sterile scissors, and digest with dilute 'antiformin.' We found, however, with bone especially, that twenty-four or forty-eight hours were necessary for complete digestion, and as our results were all negative, we were led to believe that in some instances, at least, the virulence of the tubercle bacilli had been destroyed by this prolonged treatment. Accordingly, we now employ entirely the older and simpler method of grinding the minced tissue in a sterile mortar, making an emulsion with sterile physiologic salt solution.

"We make all inoculations intraperitoneally, injecting 3 to 5 c.c. of fluid or emulsion. In this again we have found, in a large series, that the old method has many advantages over some of the later 'short-cut' methods. We have tried injecting directly into the liver and also into the groin, traumatizing the inguinal glands, but feel that the advantage gained in the few instances of early diagnoses is outweighed by the uncertainty caused by the doubtful and negative results.

"The animals that we use are usually guinea-pigs. But the orthopedic surgeon must also remember that in young people, especially, infection may be with the bovine type of tubercle bacillus, and to this the guinea-pig is somewhat resistant. The rabbit, however, is very susceptible to bovine strains and resistant to the human type of organism. In some instances then both rabbits and guinea-pigs should be injected.

"Each animal is tagged in the ear with a metal tag bearing a serial number, weighed, and a record made of his color markings from head to hind feet. It is then isolated in a small metal cage. Observations at frequent intervals reveal evidence of disease or loss in weight. Death occurs in from three to ten weeks. If it does not die, it is killed in eight to twelve weeks and a necropsy performed. The pathologic findings are striking. The spleen is nearly always greatly enlarged and studded with tubercles. The liver also is often the seat of disease, and at times the parietal peritoneum is dotted with miliary lesions. By cutting into the spleen and spreading the material from a tubercle on a glass slide, the acid-fast bacilli can be demonstrated by the ordinary carbolfuchsin stain."

The confidence we may place on any given test depends upon its accuracy. It is known that although the guinea-pig is the laboratory animal most susceptible to tuberculosis, it very seldom, if ever, develops tuberculosis unless directly inoculated. It is held that, if the material to be tested contains the tubercle bacilli, and if this material is injected intraperitoneally, the guinea-pig will develop peritoneal tuberculosis.

A negative test merely means that the injected material was not tuberculous.

In certain localities many of the cases of tuberculosis in children are said to be of bovine type. Fraser[3] reports that close to 70 per cent. of tuberculosis, as encountered in the Children's Hospital of Edinburgh, is due to the bovine tubercle bacilli, and for this blames the poor milk supply. If it is true that in Edinburgh the percentage of infection with the bovine tubercle bacilli is so high, it is probable that in this country we also have a high percentage of the bovine type of infection. While the guinea-pig is not immune to the bovine type, still it has not the same high susceptibility that the rabbit has. For this reason, when the material is obtained from children our tests are now being checked by rabbit injections. In our Clinic, however, the tuberculous patients are largely adults, and the necessity for the rabbit injections is not so frequent as it would be in children's hospitals.

Of this series of 143 patients, negative results were reported in 103. Many of those giving negative results were undoubtedly suffering from tuberculosis. Probably if we had repeated our tests with non-antiforminized material, many would ultimately have given positive results. In some it was impossible to obtain more material, and in others it was not considered necessary as the diagnosis was plain or the line of treatment so clearly defined. The use of antiformin to rid the fluid or tissue of mixed infection was responsible for many negative results. Until we discontinued this and merely made a saline suspension for injection our results did not check up with our clinical and pathologic diagnosis. The associated bacterial infections are rarely virulent enough to kill the guinea-pig. To place a definite value on a negative test is a little difficult. We feel that in a condition which is at all doubtful we must have at least three negative tests. As long as there is any doubt about the disease being tuberculous, when practicable, as in superficial joints, fluid should be withdrawn and tested at intervals. The value of negative tests increases with their number.

The test has enabled us to make positive diagnoses of suspected cases and to corroborate our diagnoses in operated cases of doubtful etiology. In many instances it is hard for patients to believe that the comparatively mild symptoms they have at the time of consultation are due to tuberculosis. A positive test is convincing evidence. The patient realizes the seriousness of his disease and aids the surgeon by his ac-

quiescence to protracted treatment and to rigid supervision of his mode of living.

CONCLUSIONS

1. As a test the intraperitoneal inoculation is practicable and requires no special laboratory facilities. The test has been of great value to us in doubtful cases, and in instances in which it is possible to obtain the material for inoculation, has become a routine procedure.

2. A positive bacteriologic test in obscure lesions makes the diagnosis certain.

3. The value of negative tests increases with their number.

4. Antiformin digestion of tissue acts on the tubercle bacilli either to kill them or reduce their virulence so that the low resistance of the guinea-pig will be sufficient to overcome them. It greatly reduces the value of the test and should not be used.

REFERENCES

1. Jones, R.: "Notes on Derangements of the Knee," Ann. Surg., 1909, i, 969–1001. "Internal Derangements of the Knee," Lancet, 1914, ii, 297–300.
2. Lane, Sir W. A.: "The Surgery of the Internal Semilunar Fibro-cartilage," Clin. Jour., 1900, xvi, 103. "Some of the Common Injuries of the Knee-joint and Their Consequences," Brit. Med. Jour., 1911, i, 537–539.
3. Fraser, John: "Etiology and Pathology of Bone and Joint Tuberculosis," Jour. Amer. Med. Assoc., 1915, lxiv, 17–23.

TECHNIC

A WATER-COOLED RETRACTOR FOR USE WITH A CAUTERY IN THE MOUTH *

GORDON B. NEW

Adequate protection of the lips and cheeks is essential in the treatment with a cautery of malignancy in the mouth. Protection is especially needed when heat is applied for a long time. The water-cooled

Fig. 396.—Water-cooled retractor in place; wooden spatula protecting tongue preparatory to cauterization of epithelioma, alveolar margin, and cheek.

retractor herein illustrated fulfils requirements, at the same time giving good exposure in the cauterization of growths on the alveolar margin.

* Reprinted from Jour. Amer. Med. Assoc., 1917, lxviii, 1253.

The portion of the retractor coming in contact with lips and cheek consists of two layers of metal with a space between for the passage of water. The water passes in and out at the distal end of the handle of the retractor.

Soldering irons or an electric cautery may be used with this retractor,

Fig. 397.—Water-cooled retractor (anterior view).

Fig. 398.—Water-cooled retractor (lateral view).

thus eliminating the necessity of a water-cooled jacket on the cautery handle. In this way a better view is obtained of the growth and the point of the cautery.

A wooden spatula is also used to protect the tongue in cauterizing growths of the jaws and cheeks.

THE TECHNIC OF TONSILLECTOMY *

E. FRANK CHASE

Since Rosenow suggested to the medical profession that the tonsils may act as foci of infection, their complete removal with the capsule intact has steadily increased in importance until we now believe in resorting to surgical interference whenever we are dealing with a disease which is focal in origin and from which all other foci can be reasonably excluded.

By surgical interference we mean the complete removal of the faucial tonsil within its capsule, including the plica at the base which carries with it many lymphoid follicles. As has been repeatedly demonstrated, this plica is capable of reinfecting or keeping up a general infection which clears up when the offending plica with its infected lymph-follicles is removed.

Many operations with varied technic have been devised, which in the main, in the hands of their originators, give satisfactory results. In view of this it would seem desirable that each operator should use and perfect the technic which to him seems most logical and best adapted to his individuality. The technic originated and perfected by Matthews is of wide application, ease and rapidity of execution, with the minimum of discomfort for the patient. This operation has been used at the Mayo Clinic for the removal of tonsils in toto in more than 10,000 cases, with a high degree of satisfaction. The ages of the patients ranged from five to seventy-five years; their mental, physical, and personal characteristics varying as much as it is possible for the mind to conceive. Many patients whose general condition precluded the use of a general anesthetic have been operated on with safety by this method. The operation has the advantage over many others in that it is applicable to various types of tonsils, such as the small, flat, submerged, and the large pendulous, as well as those firmly bound down by old quinsy scars,

or the cicatrices of one or more previous incomplete, and often mutilating, operations.

As a general rule, all patients of twelve years or older are operated on with local anesthesia. However, many children from seven to ten years of age and a few from five to six have been operated on with local anesthesia. The latter were well trained in obedience and had faith and confidence in the operator. All patients operated on with local anesthesia are instructed to eat their usual meal beforehand and to appear at the appointed time.

With assurance on the part of the operator, the patient is subjected to two brushings of the tonsils with a cotton-tipped applicator dipped in a 10 per cent. solution of cocain, an interval of five minutes being allowed between the first and second brushings. Five minutes after the second application the patient is transferred to the operating room, where sterilized instruments and solutions have been prepared. The patient is seated in an ordinary white enamel operating chair, both feet resting squarely on the floor, and requested to look the operator in the eye and to breathe naturally. The tongue is gently depressed, and from 2 to 2½ drams of a 0.1 per cent. cocain solution, to which has been added one minim of adrenalin chlorid solution, 1/1000 to the dram, is carefully injected between the capsule of each tonsil and the pillars with a Matthews syringe.

Immediately thereafter, when cocain is used, and a minute or two after when novocain (the solution preferred) is used, the tongue is depressed with a tongue depressor until the anterior pillar is distinctly outlined at its origin at the base of the tongue. The blunt point of a Robertson knife is inserted into the triangular space formed by the taut anterior pillar, the base of the tongue, and the tonsil, and carried between the anterior pillar and capsule of the tonsil, up and over the superior pole, after which it is caused to descend between the posterior pillar and tonsil. The upper pole of the tonsil, including the capsule, is now grasped with a modified Richard forceps and traction made toward the median line of the pharynx; at the same time the superior constrictor muscle with its fascia and the venous plexus of the pharynx is gently pushed away from the tonsil with the Robertson knife in such manner that the glossopharyngeal nerve does not sustain injury. The dissection is carried to the base of the tongue; a Tidding snare armed with No. 7 piano wire is looped over the forceps and continued over the dissected tonsil to the base of the tongue when the wire is sent home.

The technic of removing the second tonsil (both tonsils are always removed at one sitting) is the same as the preceding. The throat is then inspected for any remnant of lymphoid tissue remaining in the so-called plica at the base of the tongue on either side. If present, the operation is completed by grasping the remnant of tissue with a tonsil forceps and removing it with a snare or with Prince's scissors. The fossæ are dried with absorbent cotton and tincture of iodin applied, thus controlling capillary hemorrhage. The mechanical application of the iodin accelerates both venous and arterial hemorrhage, either of which can be detected as a red area on a brown background and can be readily picked up by a hemostat and pinched or ligated as the judgment and experience of the operator dictate.

THE TECHNIC OF SPLENECTOMY*

DONALD C. BALFOUR

The more frequent recognition of certain chronic disorders of the blood, particularly splenic anemia, hemolytic jaundice, and pernicious anemia, and the therapeutic value of splenectomy in these and other diseases, have recently greatly extended the indications for splenectomy and suggested some observations on the technic of the operation. In our experience (especially in those cases in which technical difficulties are encountered) the óperation has been facilitated by following a routine plan and by the precision with which the details of such a plan are carried out.

Through a left Bevan incision (Fig. 399), its length depending on the size of the spleen, the abdomen is explored. The suggestive frequency with which jaundice, attacks of epigastric pain simulating biliary colic, cirrhosis, and gall-stones, occur in many of the diseases for which splenectomy is advocated necessitates an accurate record of the condition of the liver, gallbladder, and bile-passages. Such observations will ultimately possess specific value in the elucidation of the obscure but unquestioned intimate relationship between the spleen and the liver.

The dislocation of the spleen from its position against the diaphragm and the left kidney (Fig. 400) should be the first step in the actual removal of the organ. The separation of the diaphragmatic adhesions can usually be safely accomplished by the fingers. If it is found that the adhesions have acquired blood-vessels of sufficient size to require ligation, it is then even preferable, in most cases, to postpone such ligation (unless the vessels be reasonably accessible) until the spleen has been removed, the bleeding being temporarily controlled by a gauze pack. In an occasional case, however, adhesions cannot be stripped with safety, and they must be divided between long curved forceps, care being taken to engage only the adhesions in the clamps. Hart-

mann and others have advised that the operation be abandoned when these adhesions appear formidable. However, we have not recently found such conditions to be prohibitive to splenectomy, although in some cases absolute hemostasis has been secured with considerable effort.
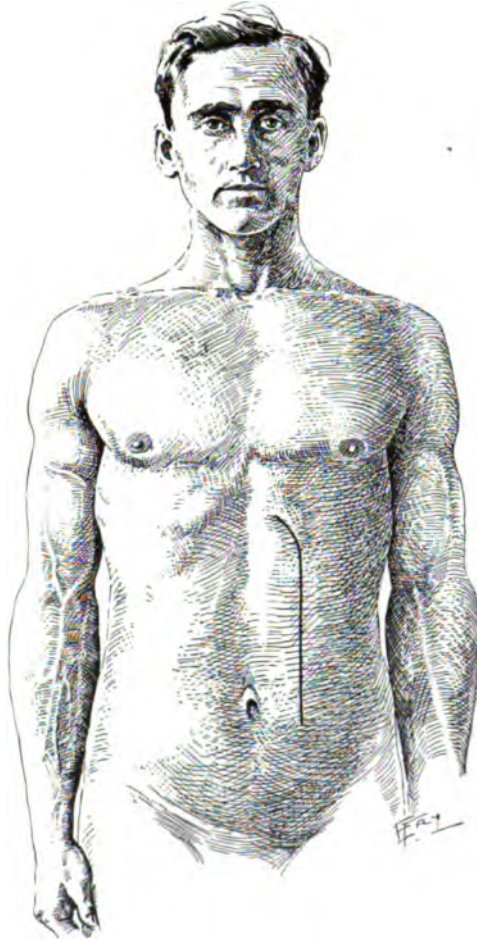
Fig. 399.—Bevan incision as adapted for splenectomy.

As soon as the spleen has been dislocated a long, hot abdominal pack is efficiently arranged in the space formerly occupied by the spleen, until the entire area with which the organ has been in apposition is under firm pressure by the gauze (Fig. 401). This accomplishes two purposes: First, and most important, the oozing surfaces are compressed

and, as the bleeding is usually venous, it is controlled without subsequent ligation if the pack (a point emphasized by W. J. Mayo) is left undis-
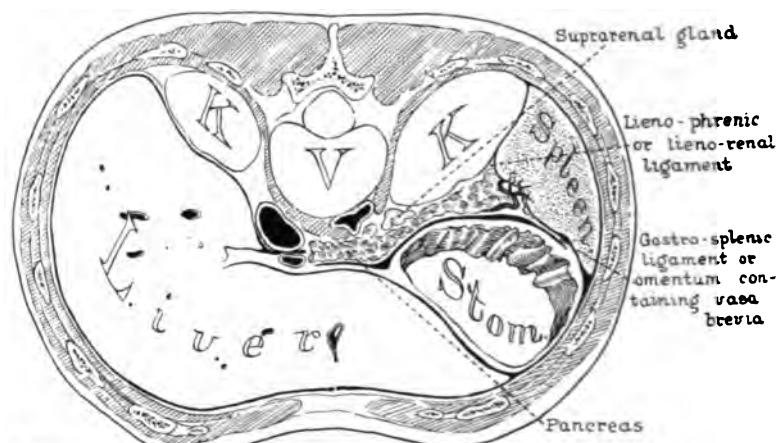
Redrawn from Toldt's Anatomy

Fig. 400.—Diagrammatic representation of the important surgical relations of the spleen.
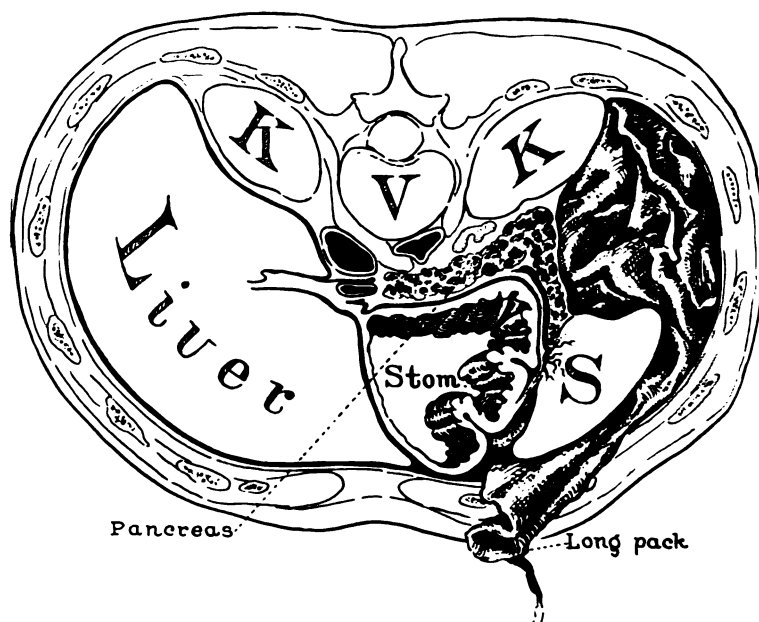
Fig. 401.—Position of the gauze pack.

turbed until the actual operation is completed. Second, an excellent support is provided for the safe manipulation and mobilization of the organ, the division of adhesions, and ligation of the main pedicle.

The spleen having been elevated in this manner, its further connections are the main splenic pedicle with its peritoneal investment (the lienorenal ligament), the gastrosplenic omentum, and in splenomegaly of long standing, various adventitious adhesions. The most satisfactory isolation and treatment of the splenic pedicle are obtained by the preliminary division of the accessory adhesions, as well as the peritoneal attachments and reflections. The gastrosplenic omentum should first be divided, in sections as close as possible to the spleen, between ligatures. The only named vessels encountered are the vasa brevia, which arise from the splenic artery at variable points, pass to the greater curvature of the stomach in this peritoneal fold, and finally anastomose with the left gastro-epiploic. In dealing with the upper edge of this gastrosplenic omentum it must be remembered that here the fundus of the stomach is normally in very close apposition to the spleen. It is necessary, therefore, always to determine the exact relationship and protect the stomach from injury in its separation from the spleen. In an earlier experience I accidentally included in a clamp and excised a small area of the wall of the stomach, the resultant opening, however, being readily closed without post-operative complication. At the lower pole of the spleen there is an occasional fibrous attachment derived from the phrenocolic ligament which, with the other adhesions, should be separately ligated.

The spleen may now be further mobilized by careful dissection of the peritoneal and fibrous coverings of the splenic pedicle. The localization of the tail of the pancreas is the important feature of this mobilization, and as the relationship of the organ is not constant, it is necessary to inspect it in all cases. In some instances the tail is short, lying against the renal surface of the spleen on the posterior aspect of the pedicle, and it may be fitted so closely into the hilus of the spleen as to have acquired a concave edge. In other cases the tail is attenuated; it is in front of the splenic vessels, and in contact with the gastric surface, while often it does not extend into the operative field.

Fig. 402 shows the spleen "turned turtle" and represents a frequent relationship of the pancreas to the splenic pedicle. It is quite obvious that such a pedicle would not be ligated without including a portion of the pancreas. Fig. 403 shows that with the reflection of the lienophrenic ligament a better exposure is obtained of the tail of the pancreas; that it can be detached from its original position by dissection and allowed to drop back from the hilus of the spleen.

tracted toward the midline. The extent to which the spleen can be lifted out of the abdomen by careful traction is surprising, if following the division of the peritoneal and fibrous investments of the pedicle, certain of the lateral venous trunks are separately isolated and divided between ligatures (Fig. 403). It should again be emphasized that cau-
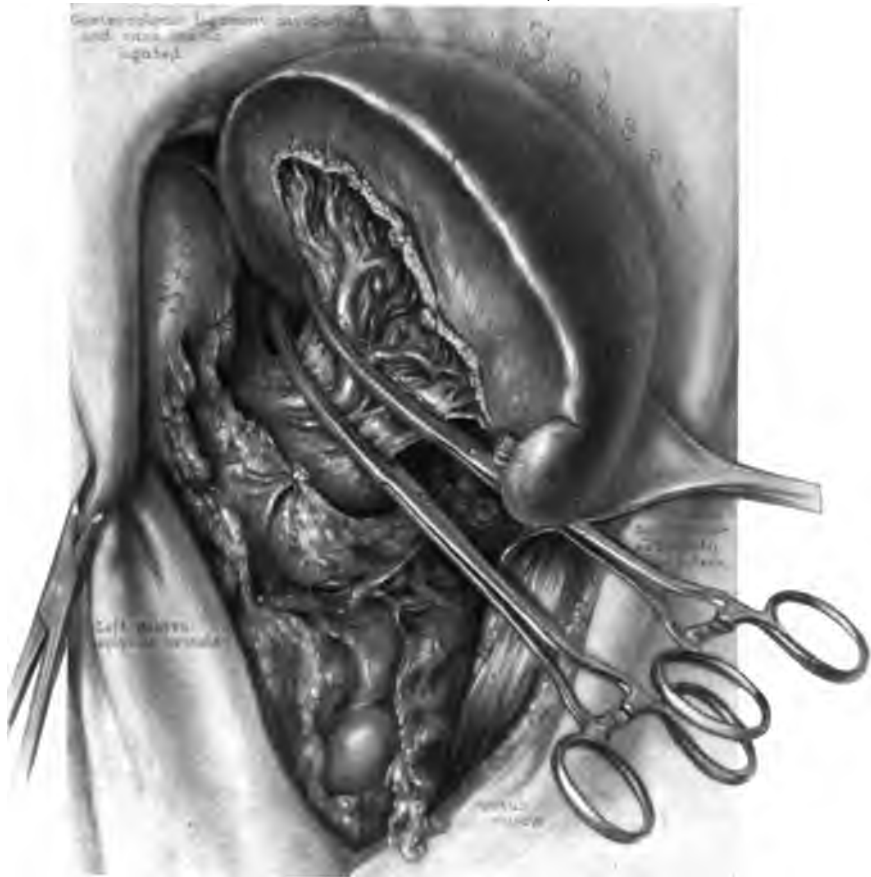
Fig. 404.—Peritoneal attachments separated, mobilizing spleen and permitting application of clamps. Pedicle to be divided at dotted line.

tion must be exercised in the degree of traction to which the pedicle is subjected and in the dissection of these veins. It is chiefly because of the normal tortuosity of the splenic artery that this elongation of the pedicle is possible, and thus facilitates its secure ligation. We have recognized the advisability of first securing, where it is possible, the ar-

terial supply, so that the spleen may partially empty itself of its contained blood through the unclamped veins before these are ligated.

If, on account of the arrangement of the veins and arterial branches, ligation in sections is not advisable, ligation en masse by the two-clamp method will prove a satisfactory and safe method. Two curved clamps are arranged on the pedicle with a third clamp on the splenic side to control "back bleeding," and the spleen is removed. A double strand of No. 2 plain catgut is tied with moderate tension in the crushed line of the inner clamp, as a partial control, and a second strand is transfixed below the distal forceps as the actual control.

Having made certain, by either of these methods, that the pedicle is securely ligated, the large hemostatic pack is removed, the newly exposed surfaces inspected, any oozing points being separately secured by fine catgut on a needle, and absolute hemostasis assured.

The disease or condition for which splenectomy is done governs largely the technical difficulties and risk of the operation. I have found, for example, that in pernicious anemia the removal of the spleen can be accomplished with comparative ease and safety. Although enlargement of the organ has been present in those cases in which we have advocated surgical treatment, adhesions are few and usually insignificant. The pedicle is, as a rule, small, and in a relatively small percentage is its treatment complicated by the relationship of the pancreas. Furthermore, the risk of the operation in this disease can be minimized by intelligent pre-operative treatment and observation, as well as by the careful selection of the cases. There must be a rational basis upon which splenectomy in pernicious anemia is advocated, as well as strict recognition of the limits of operative safety. Splenectomy is definitely contraindicated during an acute crisis, or in a period when the patient shows a steady decrease in hemoglobin and red blood-cells or when mental torpor, cord changes, and edema mark the terminal stages of the disease. Repeated transfusions from a suitable donor will frequently carry the patient through most critical exacerbations of the disease and the proper interpretation of the reaction following transfusion is essential. Further, it is important that a satisfactory donor be available after operation.

In splenic anemia splenectomy is associated with a higher operative risk and greater technical difficulties than it is in any of the more common diseases of the spleen. In the cases I have seen the spleen has been usually of large size, the vessels very friable, and adhesions occasionally troublesome. Patients in the late stages of the disease are prone to

develop fever, ascites, cirrhotic liver, or severe anemia, which conditions contribute to the seriousness of the operation. The only instance in which I thought it inadvisable to attempt splenectomy was in splenic anemia with great ascites, atrophic cirrhosis, and aneurysmal splenic vessels. The friability of the veins in this disease was especially demon-strated in a baby twenty-two months old, upon whom I performed splenectomy for typical splenic anemia of the adult type.

The operation in hemolytic jaundice is of relatively little risk and there has been no particular difficulty in the removal of the spleen, al-though the organ is occasionally very large. It is, however, most im-portant to avoid splenectomy during an exacerbation of the symptoms. Of the cases I have seen of this disease, the only operative death occurred in a patient in whom I failed to realize the import of a subacute and sub-siding acholuric crisis.

In those cases of cirrhosis of the liver associated with splenomegaly in which splenectomy is to be considered the spleen is often firmly ad-herent, and this fact, together with the poor general condition of the patient, makes the operation rather hazardous. Nevertheless, in the cases we have selected for operation, there has been no operative mor-tality; and in two cases of my own most striking benefit has thus far followed the removal of the spleen.

In the rarer conditions, such as syphilitic spleen and idiopathic splenomegaly, the operation itself is not of great risk. It has been in-teresting to note the result of splenectomy in two cases of splenomegaly with specific history and positive Wassermann. In both of these it had been previously possible to obtain a negative Wassermann by salvarsan, but it would become positive on discontinuing the treatment. Since splenectomy the Wassermann has remained negative.

From my own experience I have found that the features to be empha-sized in the technic of splenectomy are: (1) The abdominal explora-tion; (2) the dislocation of the spleen; (3) the use of a hot gauze pack; (4) the protection of stomach and pancreas from injury; (5) the pre-liminary ligation of adhesions; and (6) the treatment of the splenic pedicle.

REMOVAL OF THE RIGHT COLON: INDICATIONS AND TECHNIC *

CHARLES H. MAYO

For many years the indications for the surgical treatment of mega-colon, tumors, fistulas, and some diseases of the colon have been definite. The principles involved and the technic employed have been carefully considered along lines of theoretic, experimental, and practical develop-ment. The results of cure or relief within the natural limitations of the character and the extent of the diseases have been excellent. Within a few years still greater progress has been made in our knowledge of diseases of the colon, largely because of the endeavor to treat surgically not only stasis as an entity, but also various acute and chronic diseases, general and local, resulting from it, or, when other cause is not apparent, presumed to result from it. Thus, in chronic changes in the circulation, such as endarteritis, in the nervous system, such as in epilepsy and neurasthenia, in muscle degeneration, rheumatoid arthritis, enteroptosis, and various chronic so-called toxic diseases, surgical treatment by re-moval or short-circuiting the bowel was along lines already developed for the removal of tumors or the treatment of obstruction.

These theories have been developed mainly by the work of Lane,[1] who in short-circuiting and removing the colon made practical applica-tion of the view of Metchnikoff, namely, that the bacterial flora of the colon is responsible for many of the chronic ills of man, and that if it were possible to eliminate or shorten the colon, these ills would be decreased. There is just enough truth in this theory and sufficient that is not true to require years to standardize the diseases and conditions between the border lines of medicine and surgery, in which the elimination of the colon will give sufficient improvement over the results of therapeusis

to justify such surgical intervention. This period will be reached only when the collective judgment of physicians can select the proper cases. While Lane may be overenthusiastic in his claims, he deserves credit for much of the knowledge of the physiology and disease of the colon possessed by the medical profession today. There is no controversy concerning operations for tumors and for obstructions.

In properly selected cases of constipation great benefit can often be obtained by the surgical elimination of the absorbing area of the colon. It is certainly not advisable for simple constipation, but is advisable for some selected severe cases in which the patients are disabled by the condition in spite of prolonged and varied treatment. At the present time the patients considered suitable subjects for this procedure are those who are toxic from the condition, the drugs or the absorption of unpassed intestinal contents after taking physic, and in whom the roentgen ray shows a stasis of from three to four days' duration, which is often associated with complicating chronic infections.

We have performed general colectomy in a few cases, and the right or partial colectomy in a larger number, and we believe that except in cases in which there are tumors and local disease, the latter operation is as good for the relief of symptoms as the general colectomy. First, it removes the greatest absorbent surface in the colon; second, it is not so severe an operation, and third, it preserves the omentum, the loss of which is a serious consideration in itself, reducing protection, warmth, mobility, and the equalization of the abdominal circulation. The general colectomy often apparently leads to matting adhesions of the anterior layers of the intestine. In some cases, as reported by Clark,[2] these adhesions cause serious disability and in many cases require further operation and occasionally result in death.

It is true that much of the present-day surgery has been taken from fields formerly classified from the therapeutic standpoint as medical, and in the slow process of change the surgeon has been held in check by a constant dispute of the ground. Specialists have been developed who treat the stomach, the first portion of the intestine, and the upper abdomen, and others who devote their attention to the lower end of the colon and pelvis. Thus it is that several yards of bowel have been left as an unclaimed field—not only unclaimed, but not wanted—and this has been forced on the surgeon for the relief of numerous chronic ailments, many of which are incurable.

In judging the probable or possible benefits of the surgery of necessity

or expediency, the development and function of the large bowel should be taken into consideration.

Like the stomach and urinary bladder, the colon has a shorter heredity than the small intestine. Originally it was equipped on its right side with absorbing villi, like those of the small intestine, which disappeared early. The first portion of the colon is an absorber of fluids which are taken through the portal circulation, while the left half of the colon, especially its lower portion, has become, through convenience, an organ for the storage of the drier fecal matter. It is the natural habitat of several microbes, the activities of which produce a considerable part of its fecal contents. Such bacteria are harbored throughout life; consequently, a considerable degree of immunity to them is natural to the individual even when they become misplaced. Several diseases chronic in character, local and general, are caused by varieties of intestinal bacteria and protozoa which are not sufficiently common for the development of immunity.

The lymphatics of the colon are limited in comparison with those of the small intestine, which are very numerous. Reasoning from the nature of the contents of the colon, the converse would appear to be true; but, as I have pointed out,[3] it is probable that the lymphatic supply was limited so that the septic colonic contents might be passed through the liver. This provision of nature explains why malignant diseases of the colon remain localized for such long periods as compared with malignant diseases of the small intestine. Butlin[4] shows that in about 50 per cent. of patients with malignancy of the colon the disease at death is still local. In young persons, however, the lymphatics are more active, and earlier distribution of the disease is evident. This is true also of cancers located in the transverse colon with its associated omental glands.

The entrance of the small bowel into the colon is closed by the ileocecal valve, which is rather badly constructed mechanically, and often ineffective. By one series of observers it is looked on as acting to delay the passage of the contents of the ileum until further time is given for absorption of nutriment. Simple constipation has been relieved by enlarging the ileocecal valve (W. J. Mayo).[5] Others believe the valve acts to prevent the entrance of gas and bacterial products from the colon to the ileum, whose absorbing villi do not have the liver for a purifying agent, and some surgeons operate to reconstruct the valve (Kellogg).[6] Symington's[7] description of the valve shows that its inefficiency is due

largely to the obliquity of its entrance into the cecum; also to its lower attachment to the inner cecal wall and partial invagination into the cavity of the large bowel. In this respect it forms a mechanical barrier against back-flow such as is formed by the mechanism of the common-duct entrance into the duodenum and the entrance of the ureter into the bladder. The viscus under tension compresses the duct entrance and requires at all times some muscular effort at delivery of its contents. Peristalsis of the intestine is stimulated by the intestinal content and varies with its variety or irritating qualities. In the small intestine it is fairly regular and constant until the bowel is emptied. This propelling effort is accomplished by the action of the circular and longitudinal intestinal muscles. The peristalsis of the colon differs from the peristalsis of the small intestine in that it is not constant; the fluid contents of the ileum passing into the cecum remain at rest for a considerable period of time until consistence is increased by the absorption of fluid. Metchnikoff is undoubtedly right in his claim that in health a great portion of the body fluids are absorbed from the large bowel. The cecum normally empties but a few times in twenty-four hours. In the large bowel these movements are usually accompanied by an audible gurgling. In the right colon a slight reverse peristalsis has been demonstrated which favors delay. Delay in the right colon is due to the attachment at the splenic flexure, which forms a simple kink-valve or bend in the tube. This must be of importance as it is the most constant attachment of the colon. Rising nearly as high as the entrance to the stomach, it prevents siphonage. The fact that the intestine is a muscular tube within a muscle-walled cavity makes all operations which depend for drainage on gravity ineffectual in the majority of instances. Peristalsis of the colon is also stimulated by the intestinal contents, the movement of which is caused by contraction of the circular fibers for steadying and pushing, and aided by the sacculations. The latter are formed by the three muscular ribbons, which are one-sixth shorter than the total length of the large bowel. In the forward movement of the thicker intestinal contents the muscular ribbons serve as tractors. Space is made for the advance by the distention of the intestinal walls by the gas normally present. Thus a cecal sigmoidostomy will drain if the obstruction is above the cecum. Without obstruction, it may make a vicious circle. For various reasons the operation has been unpopular. A few patients, however, have been reported as benefited by it.

It has been shown that there is a wide variation in the length and size

of the intestine in different persons; the shortest intestine on record was 8 feet long, and the longest, 33 feet (Lynch and Draper[8]). We thus have the extreme carnivorous type and the herbivorous type. While all of the colon can be sacrificed with the maintenance of approximate good health, the loss of more than one-half of the small intestine is most serious.

The large bowel originates on the left side of the abdomen, the cecum rotating around the abdomen from left to right. At about the third month it is beneath the stomach and later rests beneath the liver and over the right kidney, until shortly before birth, when it descends to its final position in the right iliac fossa. Occasionally, according to Treves,[9] this descent may be delayed up to two years after birth, and rarely the rotation may not occur or the cecum may be permanently fixed over the right kidney. According to the period of descent it may ride over the top of the parietal peritoneum, developing a long mesentery, the "cecum mobile" of Wilms, or it may burrow through it, covering itself with an extra layer of peritoneum. Between these two extremes and the normal are the various forms of veils, adhesions, and fixations as supporting ligaments described by Long,[10] Jackson,[11] Pilcher,[12] Gerster,[13] Gray,[14] Pringle,[15] Binnie,[16] Eastman,[17] Flint,[18] and Lane. It is at once evident that, because of the rotation, all vessels and nerves of any importance are to be found on the inner leaf of the mesentery, the outer fold being principally fixative. Division of the latter adds greatly to the mobility of the bowel without impairing its vitality and simplifies some operations on it.

In the development of the intestine the vitelline duct (or should a remnant be left, a Meckel diverticulum) is attached to the ileum about $2\frac{3}{4}$ feet from the ileocecal valve (Cunningham). Embryologically, then, the lower ileum is developed with the colon.

It is to be noted that in those operations in which the colon is removed—for example, Lane's operation—or in which in certain diseases it is rendered completely functionless for considerable periods by means of a low ileostomy, as advocated by Brown,[19] the lower ileum becomes dilated and takes the place of the colon. Clark shows the dilatation of the ileum to be regular following colectomy. In low ileostomy the fluid contents of the ileum soon thicken, and emptying occurs at intervals with less gas and little odor.

TECHNIC

In operating on the right colon an incision is made in line with and through the right rectus. It should be ample in length to give free working space. Following a cursory examination of the right colon, a general exploration of the entire abdomen should be made to search for metastases in malignancy and also to avoid overlooking associated disease, thus preventing useless or unnecessarily extensive operations in malignancy or failing to make them sufficiently extensive.

If extirpation is decided on, extensive protective gauze packing is adjusted to the inner side of the colon. An incision is made along the white fold of parietal peritoneum where it joins the peritoneal covering of the outer side of the colon. This permits of extreme mobility and allows the bowel to be elevated outside of the abdominal incision. The space to the outer side is filled with a protective gauze pack. The ileac mesentery is perforated, and the ileum is divided between double clamps three inches from the ileocecal valve, the cut ends projecting from the forceps being sterilized with the actual cautery. From below up, the mesentery of the cecum and ascending colon is divided between forceps up to the transverse colon, and the omentum is ligated and separated from the right one-third of the transverse colon (Fig. 405). At this point the colon is divided between clamps, the loose bowel removed, the projecting stump from the distal clamp also being treated by cautery. The vessels supplying this region, few in number and readily seen, are ligated with catgut. In non-malignant cases the division of the mesentery is made closer to the bowel, while in malignancy more of the mesentery is taken, including the lymph-glands which drain the area. Care should be taken in the separation of the colon to avoid injury to the duodenum. While the ureter should be observed on the right side, it does not come into the operative field except in extensive malignancy, when ligation of the ureter or removal of the kidney may be necessary. We have been able to remove such advanced tumor growths in numerous instances, including several in which the patients had been explored and declared inoperable from one to several months previously. In the latter type of cases the tumors are usually adherent to the incision in the abdominal wall and require a block removal of the entire area over the growth. In such cases there is greater danger of recurrence in the abdominal muscles than of recurrence within the abdomen.

Using chromic catgut as a suture, the end of the colon is prepared for

closing by inserting the needle and catching into the bowel first on one side and then the other over the forceps, including the peritoneum and muscle, the loops crossing the forceps being left loose. Any contents of the bowel are now forced onward, and a rubber-covered clamp applied

Fig. 405.—Removal of right colon, showing lines of section.

'16—58

for control about 4 inches from the end. The forceps closing the end of the bowel are now removed, the end opened, and the female or spring side of a proper-size Murphy button pushed through the loose sutures into the opening and left loose within the colon (Fig. 406). The two ends of the thread being drawn taut, immediately invert the mucous end of the colon and approximate the peritoneal surfaces. A second row of sutures is applied to make the closure better, the ends of the suture being left long. (Ligation of bowel end and purse-string in-

Fig. 406.—End-to-side union by Murphy button.

vagination is equally good.) The button within the bowel is manipulated so that its tube is pressed against one of the muscular bands, about 2½ inches from the end of the bowel. The bowel is incised on the tube of the button, so that it can be pushed through the wall of the intestine, no suture being used. This is held until the other half of the button is adjusted into the end of the ileum by suture. The two halves are then pushed together, making an end-to-side union. If deemed necessary, a few interrupted sutures of fine catgut or silk may be used over the

button, to adjust adjacent epiploic tags or omentum for protection and support at the point of union. The anastomosis can be made by suture,
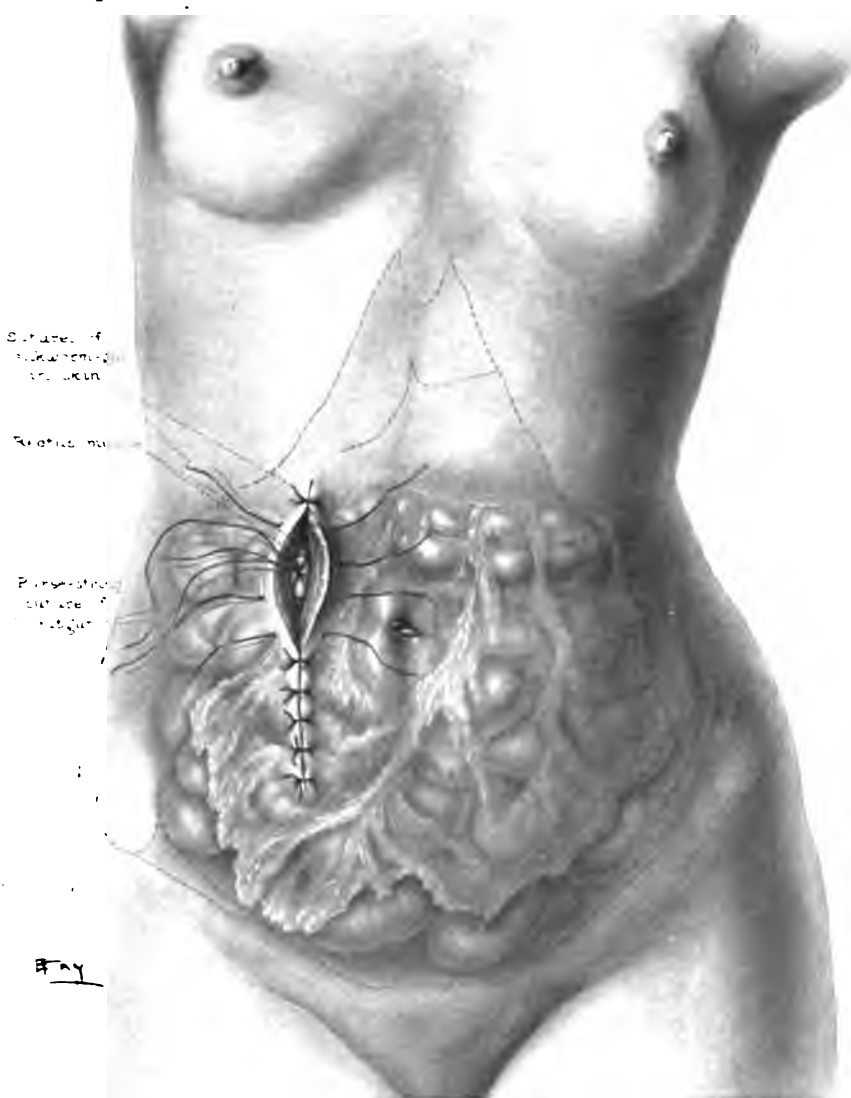
Fig. 407.—Incision, showing method of closure and end of bowel in depth of wound.

but the Murphy button is safer, quickly adjusted, and ideal for the purpose. Some prefer side-to-side union in spite of the tendency to dilata-

tion of the blind ends. The triangular opening in the mesentery beneath the union is now closed by catgut suture. A few sutures are inserted to adjust the parietal peritoneum over the exposed cellular tissue from which the colon was separated (Fig. 407). The wound is now closed, the end of the colon being drawn into the peritoneal opening as closure is made. The colon is brought into the muscle but not through it, the muscles being sutured above and below this point; the long suture from the end of the bowel hangs out of the incision. A strip of gauze is inserted to the end of the bowel to keep the muscles apart.
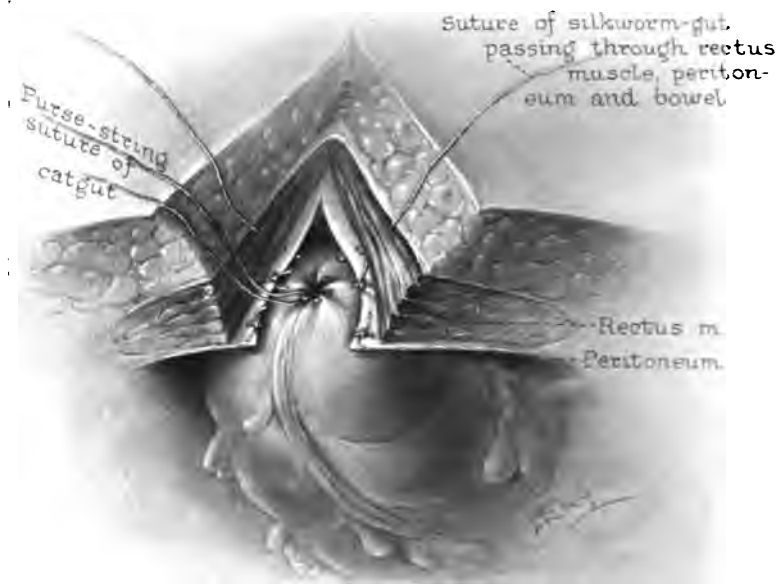
Fig. 408.—End of colon brought up to peritoneum and sutured.

The procedure is employed as a safety-valve to relieve gas should stasis with great distention occur between the fourth and sixth days. Peritonitis causes most of the deaths by necrosis of the union from distention. In a series of twenty cases we have had no deaths from the use of the Murphy button and the safety-valve method. By drawing on the projecting suture and using small pointed forceps along the taut thread, the bowel is readily opened and gases permitted to escape. If not required by the sixth day, the suture is cut, the gauze removed, and the opening allowed to close. If the suture is not needed, the healing is not

prolonged; if needed, closure is usually effected within a short time (Fig. 408). This safety-valve is of great benefit in about 15 per cent. of the cases. Should the peritoneal cavity be contaminated, drainage is secured by stab incision with drain in the loin.

The method of operation described is safe and remarkably effective for tumors, granulomas, and fistulas. In cases of toxemia the general condition is improved, and in 80 per cent. the constipation is improved. The general improvement made in the latter cases is somewhat less
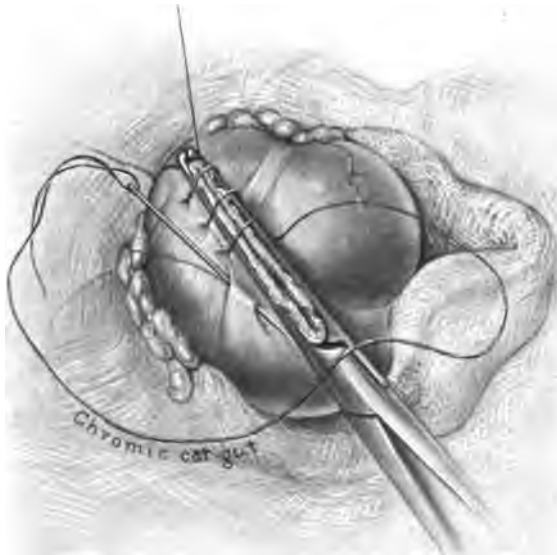
Fig. 409.—Aseptic method of inverting mucous membrane by a running suture.

marked than in operations of necessity for tumor and obstruction (Fig. 409). In operating on the left colon for obstructive conditions by the Mikulicz-Bruns method or by resection, appendicostomy is of great value.

Not including the rectum, there were 262 resections of the large intestine for malignancy. Of the patients who recovered and who were operated on more than five years ago, 54 per cent. are alive. Of those operated on more than three years ago, 67.5 per cent. are alive.

From January, 1898, to December 31, 1915, the right half of the colon

was resected for tumors, disease, and stasis in 235 cases, with an operative mortality of 12.5 per cent. In our early work the operability was lower, the mortality lower and the permanency of cure higher. This led to an increase in the operability of these otherwise hopeless cases, with the result that there was an increase in the mortality and a decrease in the permanency of cure; but considered from the standpoint of the total number of cases seen, a great increase in the number cured. The present operability is 62 per cent. Unless the operability percentage is given, statistics in regard to the results of operations for malignancy are misleading.

REFERENCES

1. Lane, W. A.: "Chronic Intestinal Stasis," Brit. Med. Jour., 1912, i, 989–993; Surg., Gynec. and Obst., 1910, xi, 495–500; Lancet, 1912, ii, 1706–1708.
2. Clark, J. G.: "The Removal of the Colon for Obstructive Fecal Stasis, with a Report of Eight Cases," Tr. South. Surg. and Gynec. Assoc., 1913, xxvi, 358–392.
3. Mayo, C. H.: "Surgical Physiology of the Lymphatic System," Tr. South. Surg. and Gynec. Assoc., 1903, xvi, 442–452.
4. Butlin, H. T.: "On the Operative Surgery of Malignant Disease," Phila., Blakiston, 1900, p. 260.
5. Mayo, W. J.: "Ileocecal Orifice and Its Bearing on Chronic Constipation," Ann. Surg., 1900, xxxii, 364–368.
6. Kellogg, J. H.: "Incompetency of the Ileocecal Valve the Most Common Cause of Ileal Stasis," Lancet-Clinic, 1915, cxiii, 602–608.
7. Symington: Cited by Cunningham, D. J.: Text-Book of Anatomy, New York, Wood, 1907, p. 1078.
8. Lynch, J. M., and Draper, J. W.: "Anastalsis and the Surgical Therapy of the Colon," Amer. Jour. Med. Sci., 1914, cxlviii, 828–835.
9. Treves, F.: "The Anatomy of the Intestinal Canal and Peritoneum, Hunterian Lectures," Brit. Med. Jour., 1885, i, 415–419, 470–474, 527–530, 580–583.
10. Long, J. W.: "Pseudoperitoneal Cauls of the Colon," Tr. South. Surg. and Gynec. Assoc., 1912, xxv, 446–468.
11. Jackson, J. N.: "Membranous Pericolitis," Tr. West. Surg. and Gynec. Assoc., 1908, xviii, 269–291.
12. Pilcher, L. S.: "Surgical Aspects of Membranous Pericolitis," Ann. Surg., 1912, lv, 1–16.
13. Gerster, A. G.: "On Chronic Colitis and Pericolitis," Ann. Surg., 1911, liv, 325–343.
14. Gray, H. M. W.: "Chronic Intestinal Stasis," Brit. Med. Jour., 1914, i, 188–191.
15. Pringle, S. S.: "Chronic Intestinal Stasis," Brit. Med. Jour., 1914, i, 183–188.
16. Binnie, J. F.: "Pericolitis Dextra," Month. Cycl. Prac. Med., 1905, xviii, 341–353.
17. Eastman, J. R.: "The Foetal Peritoneal Folds of Jonnesco, Treves and Reid and Their Probable Relationship to Jackson's Membrane and Lane's Kink," Surg., Gynec. and Obst., 1913, xvi, 341–353; "A Further Study of Pericolonic Membranes," ibid., 1914, xviii, 228–232.
18. Flint, J. M.: "Embryonic Bands and Membranes About the Cæcum," Bull. Johns Hopkins Hosp., 1912, xxiii, 302–311.
19. Brown, J. Y.: "The Value of Complete Physiological Rest of the Large Bowel in the Treatment of Certain Ulcerative and Obstructive Lesions of this Organ, with Description of Operative Technique and Report of Cases," Tr. South. Surg. and Gynec. Soc., 1912, xxv, 440–445.

SUGGESTIONS CONCERNING STAINING METHODS USED IN THE STUDY OF PATHOLOGIC LESIONS IN SYMPATHETIC GANGLIA [*]

LOUIS B. WILSON

In reviewing the literature of the pathology of the sympathetic nervous system recently, I have been struck by the paucity of studies on the ganglion-cells and by the fact that in the studies that have been made the tissues have been so rarely prepared by modern methods.

I wish to call attention here to some methods which it seems are not used by pathologists in the study of the autonomic nervous system, but which may give clear pictures of otherwise obscure lesions.

1. The cells of ganglionic tissue freshly removed from the living patient may be very well stained in frozen sections with polychrome methylene-blue, differentiated in salt solution, and mounted in Bruns' glucose medium.[1] The chromatin granules and the nuclei stain well. Changes in the size and shape of the cells are readily made out, and of course are free from the suspicion of artefacts due to embedding. If the sections are not too heavily stained, or if they are well washed out in salt solution, pigment-granules, when present, show up very beautifully. The character of the cells of the stroma also may be clearly observed.

2. Frozen sections of fresh tissue, or of material recently fixed in formalin, when stained with Sudan III, followed by a feeble staining with Ehrlich's acid hematoxylin, show advanced fatty changes, if present, very satisfactorily. (Plate I, c.)

3. Luden's[2] modification of Weigert's method gives good color pictures for the comparative differentiation of lipoids.

4. Bensley's[3] acetic-osmic-bichromate method for mitochondria gives not only a most satisfactory staining of these structures, but also other details of the ganglion-cells, including the lipoid granules.

919

5. Levaditi's[4] method, exactly as used for the staining of spirochetes, may be applied to formalin-fixed material, and will usually give strikingly beautiful results. For young human tissues and for tissues from experimental animals (dogs, goats, rodents), however, it is not so good as Method 6.

6. The most satisfactory of all methods for the study of advanced changes in ganglionic cells are the various modifications of Ramón y Cajal's[5] 1910 silver-impregnation methods. These are applicable to all changes of human tissue and to all of the ordinary experimental mammals. For human sympathetic ganglia, our best results have been obtained with a modification of Ramón's formula 4A.

Tissue, well fixed in 10 per cent. formalin, is placed for twenty-four hours in 95 per cent. alcohol with one drop of ammonia to each 10 c.c. of alcohol. It is then wiped off with blotting-paper, and silvered for five days in the oven at 38° C. in 2.5 per cent. silver nitrate solution. It is then washed quickly in water, and developed for two days in Ramón's pyrogallic developer, consisting of pyrogallic acid 5, formalin 5, and water 100. The tissues are then embedded in paraffin, cut and mounted in balsam. (Plate I, d.) For tissues from the goat, better results were obtained by increasing the strength of the silver nitrate solution to 5 per cent.

7. Bielschowsky's methods are similar to Ramón's, but in our hands have not given as good results on the ganglionic cells. They are of greater value, however, in the study of nerve-fibers.

REFERENCES

1. Wilson, L. B.: "A Method for the Rapid Preparation of Fresh Tissues for the Microscope," Jour. Amer. Med. Assoc., 1905, xlv, 1737.
2. Luden von Heumen, G.: "Ueber die Anwendung meiner neuen schnellen Weigert-Modification für Paraffinschnitte," Centralbl. f. allg. Path. u. path. Anat., 1912, xxiii, 385–394.
3. Bensley, R. R.: "Studies on the Pancreas of the Guinea-pig," Amer. Jour. Anat., 1911–12, xii, 308.
4. Levaditi, C.: "Sur la coloration du spirochæte pallida Schaudinn dans les coupes," Compt. rend. Soc. de Biol., 1905, lix, 326.
5. Ramón y Cajal: "Trabajos des Lab. de Investigaciones Biologicas," 1910, viii, Rev. trimestral micrografica, xiii.

PLATE I.—CERVICAL SYMPATHETIC GANGLION-CELLS STAINED BY VARIOUS METHODS.

a
Faint
Hematox.
75687
10 μ Sec.
X 400

b
Held-
Nissl
119713
10 μ Sec.
x 400
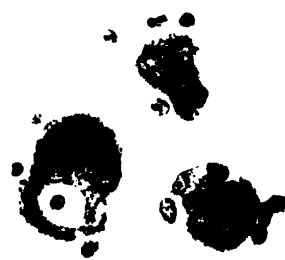
c
Faint
Hematox.
+Sudan III.
75687
10 μ Sec.
x 400

d
Ramon
y Cajal
75687
10 μ Sec
x 400

A MACHINE FOR SHAKING BLOOD-MIXING PIPETS *

GEORGE G. LITTLE

To eliminate all shaking by hand of the glass tubes used to determine the number of red and white corpuscles to a cubic millimeter in testing blood, a motor-driven machine was designed and built to duplicate the hand method as nearly as possible.

A study of the hand motion while shaking the tube was made to determine the exact movement, the number of strokes per minute, the length of time per tube, and the possible saving of time from the use of a machine.

The hand movement showed the tube to be moving through an arc

Fig. 410.—A, cube.

the radius of which was equal to the distance from the tube to the wrist, and the length of the stroke to be about two inches.

Two tubes are usually shaken at one time by the hand method. They are held endwise between the thumb and the first and middle fingers and given a rapid reciprocating movement lengthwise.

A pipet or tube (Fig. 410) has a bulb or enlarged portion near the middle containing a small glass cube, as shown at A. This bulb is open to the air through a fine hole about one-tenth of a millimeter in diameter. Through it a solution is drawn and into the solution a few drops of blood. The tube is then shaken to throw the cube from side to side through the

mixture. In this manner the blood-corpuscles are separated so that when distributed in a measured thin layer on a glass slide they can be readily counted by the aid of a microscope.

Fig. 411 shows the machine mounted on a small fan-motor. An
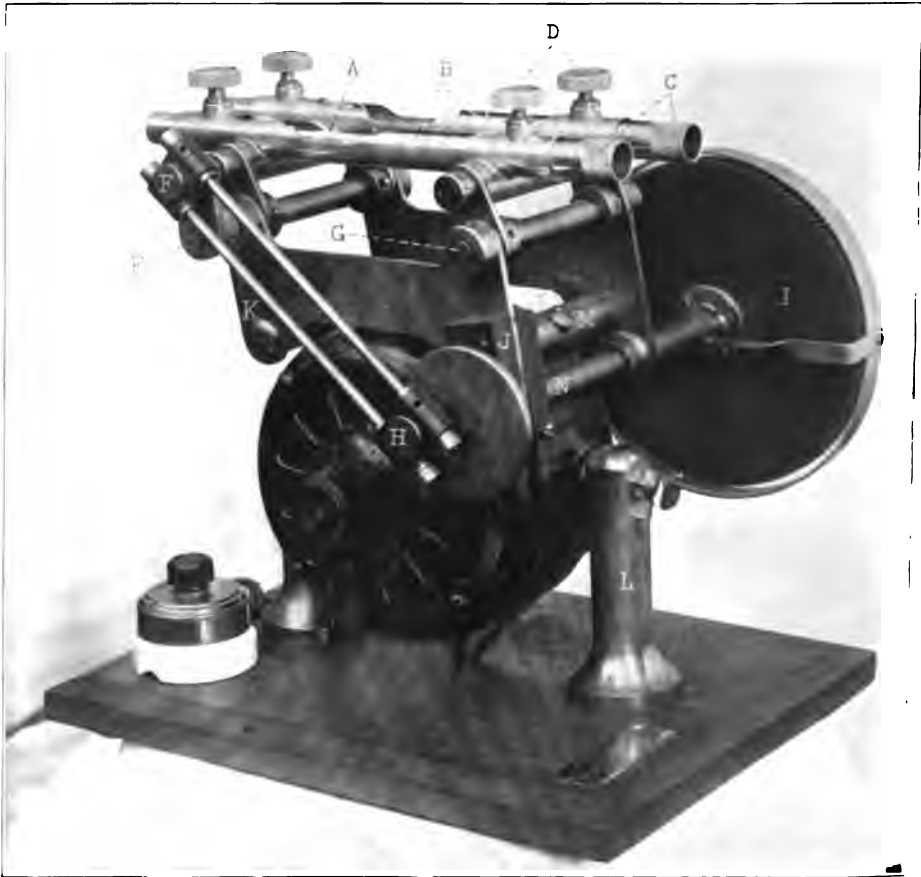
Fig. 411.—Machine for shaking blood-mixing pipets. Baseboard, 9×12 inches; height of instrument, 9 inches.

idea of size is given by the motor and the large gear, both of which are about six inches in diameter.

The pipet (A) is shown in position ready to be shaken.

The holder (B) is made of brass tubing. Lugs are soldered in place to hold thumb-screws (D), which serve to secure the adjustable slides (C) in place while the tubes are being shaken.

The inner ends of the slides (*C*) contain rubber tips which receive the ends of the pipets, pressing against and closing the holes and thus keeping the solution from being shaken out of the tube.

The holders (*B*) are secured to cross trunions bearing in the upper ends of the short arms on the shafts (*G* and *E*) and are moved through an arc. The radius of the arc is one inch and the stroke one and one-half inches.

The wrist (*F*) carries the upper end of the connecting rod which transmits the motion of the wrist (*H*) on the crank-shaft (*N*) driven by the gear (*I*), which meshes directly with the pinion on the motor shaft.

The bearing blocks (*J*) are made of fiber and are secured to the side frame (*K*). They support the crank end of the shaft (*N*) and are split at the lower ends and fitted with screws to take up the wear of the shaft.

Two space rods (*M*) secure the side plates in position on the motor as well as hold them in alinement.

The motor is supported by the two standards (*L*) which are secured to the baseboard and have lead washers underneath to deaden the slight noise of the motor and gears.

The board is nine by twelve inches and a snap switch for starting and stopping the machine makes it complete.

The installation of this machine saves the services of one assistant.

GENERAL

THE ELEMENT OF ERROR IN ABDOMINAL DIAG-
NOSIS*

HAROLD L. FOSS

A few months ago I heard a distinguished surgeon say that, had he life to live over, being fully conscious that brilliant operators are infinitely more common than great diagnosticians, he would desire to become a clinician. No more fascinating field exists in medicine than surgical diagnosis; and yet, what branch has so few masters? No less interesting are the commoner errors of surgical diagnosis, and particularly engrossing is the study of the seemingly inevitable mistakes made in the diagnostics of abdominal disease.

Absorbed with this subject, I, some time ago, at Rochester, kept record of the errors made in a series of general cases admitted to the diagnostic department of the Mayo Clinic. Eleven hundred and seventy patients were studied—about one-half of these coming to operation. With the latter group it was found at the operating table that there was a gross error in the primary diagnosis of the clinicians in 10.08 per cent. In all of these the surgical indications were correct and the patient required an operation for relief, but in the percentage stated the clinical diagnosis was wrong.

The original diagnosis, with the operative findings, in all cases in which gross errors were made were studied, but at this time only those with abdominal diseases are considered and are presented in the following table:

GROSS ERRORS IN DIAGNOSIS CHECKED AT OPERATION

CLINICAL DIAGNOSIS	OPERATIVE DIAGNOSIS
1. Perforating gastric ulcer	Chronic cholecystitis and appendicitis
2. Aortic aneurysm	Ovarian cyst
3. Chronic cholecystitis	Duodenal ulcer
4. Duodenal ulcer	Chronic appendicitis
5. Duodenal ulcer	Chronic cholecystitis
6. Duodenal ulcer	Chronic appendicitis

GROSS ERRORS IN DIAGNOSIS CHECKED AT OPERATION—(*Continued*)

CLINICAL DIAGNOSIS	OPERATIVE DIAGNOSIS
7. Chronic appendicitis	Duodenal ulcer
8. Carcinoma of the stomach	Septic gallbladder with stones
9. Duodenal ulcer	Chronic cholecystitis
10. Duodenal ulcer	Chronic appendicitis
11. Chronic appendicitis	Gall-stones
12. Pyloric ulcer	Carcinoma
13. Ovarian cyst	Hydronephrosis
14. Extension of pus-pocket from perineal abscess	Pancreatic cyst
15. Chronic cholecystitis	Carcinoma of the stomach
16. Chronic appendicitis	Hydrosalpinx
17. Ovarian cyst	Fibroids
18. Hemorrhagic endometritis	Fibroids
19. Neurosis (explore) appendix?	Chronic cholecystitis with stones
20. Reflex (explore)	Gall-stones
21. Chronic appendicitis	Chronic cholecystitis
22. Functional stomach (explore)	Strawberry gallbladder (chronic cholecystitis)
23. Duodenal ulcer	Carcinoma of stomach
24. Carcinoma of stomach	Old duodenal ulcer
25. Ovarian cyst	Hydrosalpinx
26. Pyloric obstruction (ulcer)	Chronic cholecystitis
27. Carcinoma of cecum	Chronic appendicitis with abscess
28. Gastric ulcer	Thickened pyloric ring (congenital)
29. Fibroids	Ovarian cyst
30. Pyloric obstruction (ulcer)	Syphilis of stomach
31. Intestinal obstruction; postoperative adhesions	Ring carcinoma of transverse colon

It is interesting to note that of these errors over 75 per cent. have to do with the duodenum, gallbladder, or appendix. The majority of patients with disease of one or more of these organs have an accurate diagnosis made of the condition, but, in a certain percentage, as has been shown, gallbladder disease is mistaken for duodenal ulcer, duodenal ulcer for chronic appendicitis, chronic appendicitis for gall-stones, and so on. The close relationship existing between the gallbladder, appendix, and duodenum has long been known, and Rosenow,[1] in his recent work on the elective localization of the streptococci, has added the latest data to prove the fact. Our knowledge of this and the clearer realization of the difficulties of differential diagnosis of conditions affecting these organs have rendered the spectacular McBurney's incision, with its limited exploratory field, considerably out of fashion. The list of errors presented would have been much smaller had not a straight rectus incision been made in most of the cases. The incompleteness of an operation performed through a gridiron incision on a chronic appendix, not presenting an absolutely clear picture, particularly in an adult, cannot be questioned. Such an operation leaves the surgeon in but a slightly better position than the gastro-enterologist who cures gastric and duodenal ulcer, and is kept from knowing he hasn't only by the thick-

ness of the abdominal wall. The surgeon routinely following this practice has no check on his diagnosis and will have a satisfying small percentage of errors to record.

The extraordinary similarity in symptomatology often existing between chronic appendicitis and duodenal ulcer is a subject sufficiently threadbare to be omitted were it not for the fact that the point is being constantly overlooked and is a potent factor in rendering abdominal diagnosis anything but an exact science. Not uncommonly does a patient present a history of hunger pain relieved by eating or the taking of alkalis and occurring with definite periodicity with nothing to account for the syndrome but a chronic catarrhal appendicitis. And to strengthen the diagnosis of duodenal ulcer the gastro-enterologist may report a marked hyperacidity, and the roentgenologist hyperperistalsis, or other suggestive signs; and when the operation is performed the duodenum is found normal and the removal of a chronically inflamed appendix cures the patient. I have records of several such patients in whom a 90 per cent. diagnosis of duodenal ulcer was made on a clear, uninvolved, so-called text-book history, who were completely relieved by the removal of their appendixes. One patient gained 18 pounds in the first sixty days following his operation.

Of the 264 cases of gastric ulcer operatively demonstrated at the Mayo Clinic during the year 1913–14, and studied by Eusterman,[2] there was an error in the primary diagnosis in 33 per cent. though an alternative diagnosis of gastric ulcer was made in 8 per cent. In 27 per cent. of the cases of gastric ulcer the primary diagnosis was duodenal ulcer.

Of 814 cases of duodenal ulcer observed in the same period there was an error in the primary diagnosis also in 33 per cent. In 10 per cent. of the cases of duodenal ulcer the diagnosis was gastric ulcer.

"Ninety per cent. of supposed diseases of the stomach are not entities but rather groups of symptoms masquerading as diseases and named accordingly" (Mayo). To no small extent is the converse true —that a certain percentage of actual surgical conditions affecting the stomach, duodenum, appendix, or gallbladder parade a horde of incoherent, intangible, irrelevant symptoms masquerading as nothing in particular, unless it be neurosis—the diagnosis too frequently made. Thus we are sorely in need of more accurate methods of procedure in surgical diagnosis, particularly as applied to the upper abdomen. The clinical history stands first in importance, but it is frequently unreliable. The Cammidge and other tests have become but unpleasant memories,

'16—59

though they had some value. Even with the assistance rendered by the test-meal, gastric diagnosis is anything but positive and methods of greater precision are looked for. For several years there has loomed large on the horizon the x-ray, and now to such an extent has it come to the front that it can be said with truth that nothing in the past decade has so advanced abdominal diagnosis as has roentgenology. Fluoroscopic examination, supplemented by plate studies, and, in suspected ulcer, fluoroscopic examination combined with serial plate investigations, have increased the degree of diagnostic accuracy by means of the x-ray to nearly 80 per cent. for duodenal ulcer, 90 per cent. for gastric ulcer, and over 95 per cent. for gastric cancer.

The commonest errors in abdominal diagnosis are made in connection with lesions of the gallbladder, duodenum, and appendix, but in this regard, and only second in importance, are the mistakes made in rendering a preoperative diagnosis in diseases of the urinary system. Renal and ureteral stones, often presenting symptoms simulating anything but those of the classic picture of calculi, are factors accounting for many of our diagnostic errors. Not only is the history in these cases often confusing in the extreme, but the invaluable signs, fortunately present in the majority of cases, are often absent. Thus Cabot[3] shows that in a series of 150 cases of renal and ureteral calculi the urine was entirely and persistently normal in 14 per cent., and macroscopic and microscopic blood was absent in 32 per cent. Even the x-ray is useless in a certain percentage of cases of urinary calculi, failing in 10 to 15 per cent. in Cabot's[3] series and in 11 per cent. in that of Braasch.[4]

The patient with a small ureteral stone, presenting an uncertain history, with repeatedly negative urine and nothing to show on the x-ray plate, particularly if there is a large element of neurosis in the make-up, will be frequently dismissed, branded neurasthenic, or, if he has fallen into the hands of an accommodating surgeon, will be stamped neurasthenic and simultaneously his appendix will be transferred to the formalin bottle. It is in these vague cases that the cystoscope and the pyelogram are of greatest value, and failure to resort to them often results in diagnostic humiliation. Not only in the vague but occasionally in obvious cases are gross errors made. Thus, the large clinic does not exist in which, at some time or other, one of its surgeons has not cut down upon a perfectly apparent cystic gallbladder or splenic tumor only to regret he had not a posterior incision through which to remove the hydronephrotic kidney he has brought to light.

To every clinic come a large number of patients presenting so few definite symptoms and such a vast amount of vague, indefinite, irrelevant data as to render the making of an exact diagnosis utterly impossible. To certain of these the title of neurasthenic is applied, a term often contracted by the exasperated and irreverent examiner to "neuro."

To the conscientious diagnostician these patients are especially trying, for, though the examiner may feel from the first few minutes of the conversation that the diagnosis is obvious, he lives in constant fear that in the incoherent recital somewhere lurks a point of great significance and that the definitely neurasthenic patient's symptoms may, in a large measure, be the result of some organic, curable condition which he may completely overlook. The attempt to bring clarity out of the tale of symptoms as presented by the full-fledged neurasthenic is the most difficult thing in medicine, and there is no task in the law or ministry approaching it.

To send a patient away branded neurasthenic is often to acknowledge defeat, but to dimiss the patient with that diagnosis only to meet her on the street a month later, obviously in excellent health, is to excite wonder and amazement equaled only by the shock of hearing of her operation for duodenal ulcer, gall-stones, renal calculus, or what not at the hands of a more astute brother.

The deadly boredom associated with the daily routine examination of a large number of patients, presenting a horde of symptoms, and yet having no definite organic lesion, accounts for a certain percentage of errors in diagnosis. The effect of the neurasthenic on the examiner is not only to make him less alert in the study of patients of this type, but to render him often casual and superficial in investigating the condition of persons who, though they have organic disease, possess also a large element of neurosis. This type of patient is likely to direct the thoughts of the diagnostician far afield by immediately entering upon an exhaustive recital of irrelevant matter.

In a group of over 1000 consecutive patients admitted to the general diagnostic department at Rochester, 17 per cent. were sent away with the lone diagnosis of neurosis,—17 per cent. of defeats,—and these acknowledged only after every means had been exhausted to render a more scientific decision! In this group, however, is recorded one patient as having returned for reëxamination, and, though the final diagnosis was 90 per cent. for neurosis and a bare 10 per cent. for chronic appendicitis, she was so clamorous for an operation that an exploration was performed

on the strength of the lone 10 per cent. and was promptly relieved by
the removal of her gallbladder and the 30 or 40 stones contained therein.
Such a case is an exception, however, and, although this patient had
organic disease, the symptoms were unquestionably vague, and the
picture was completely masked by the neurotic manifestations which,
in all probability, will remain to a great extent, even now that the organic
condition has been corrected. The cure of definite surgical disease in a
chronic neurasthenic does not, unfortunately, always mean the cure of
the neurosis.

Two other groups of patients, like the unfortunate and ever-present
neurasthenics, are customarily examined with less exact care than they
deserve, and the frequent superficial study of these individuals results
in very materially adding to the percentage of error in general diagnosis.
The patient whose condition is complicated by alcoholism or venereal
disease is apt to be considered with less seriousness by some and with
more or less contemptuous disdain by others, the accuracy of the final
diagnosis being regulated by esthetic rather than scientific factors.
The Wassermann has gone far in revealing to us the magnitude of the
rôle played by syphilis in human disease, and the liability of the diagnos-
tician to overlook latent lues is still another factor adding to the element
of diagnostic error. The most important conclusion to be drawn from
recent investigations in specific disease is that it is even more prevalent
than is ordinarily supposed. The demonstration that of 4000 general
hospital patients routinely subjected to the Wassermann test 600 gave
a complete fixation justifies such a belief.[5] Since in tabes, the one
syphilitic condition with which we are chiefly concerned in a study of
errors in abdominal diagnosis, only 18 per cent. give positive Wasser-
manns in the blood, the necessity, in obscure abdominal cases, even with
negative pupil and patella reflexes, of an examination of spinal fluid
is apparent.[5] Cases of unsuspected syphilis greatly outnumber those
frankly syphilitic among patients applying for treatment at a general
clinic.

In the past few years several writers, among them Cabot[6] and Hall[7]
in this country, and König,[8] Lomnitz,[9] and others in Europe, have
directed attention to operations for supposedly local abdominal disease
in patients suffering with tabes dorsalis in whom no lesion was found at
laparotomy. With the Wassermann reactions on the blood and spinal
fluid becoming matters of routine, we have learned that any imaginable
combination of abdominal symptoms may be due to cerebrospinal

syphilis. It is nearly fifty years since Charcot[10] wrote, "of all the visceral symptoms which may display themselves from the period of lightning pains, one which is the most remarkable and least known, if I mistake not, is that which I have proposed to designate by the name of gastric crisis. . . . Very often its real significance remaining misunderstood, it is the occasion of grave errors in diagnosis."

Of 1000 tabetics recently studied by Nuzum,[11] 8.7 per cent. had been subjected to laparotomy one or more times under a mistaken diagnosis. Gastric ulcer was the diagnosis most frequently made, and next gall-bladder disease, with the appendix a close third. In other tabetics on whom useless operations were performed the diagnosis ranged from renal calculi to ectopic gestation. Such mistakes are not made through clinical ignorance, but as the result of superficial examinations, with hurried history taking, in which significant data are overlooked. A history of vomiting, paresthesia, rheumatism, bladder disturbances, etc., in doubtful cases, even with normal pupils, demands a cytologic examination of the spinal fluid, together with a Wassermann.

In reducing the element of error in diagnosis to a minimum in a large series of cases, as is yearly examined in every great clinic, a system of efficiency in the department of clinical diagnosis must be developed to as high a degree of perfection as possible.

At the Mayo Clinic the new patient is ordinarily placed in charge of one man, and as many days or weeks as he may deem necessary are devoted to the study of the case. Unlimited time and effort are given to the task. Experts in laboratory procedures, in cystoscopic examination, in roentgenology, are immediately at hand, to whom the patient is sent for special study. All data are then collected and correlated by the original examiner and the diagnosis made.

In the daily routine of clinical work, many and varied physical abnormalities in the patient, as well as significant and important evidence in the history, will be completely overlooked, even by the most painstaking examiner. This alone helps to increase the element of error not an inconsiderable degree, and, in developing our system of diagnostic efficiency, must be considered. To eliminate this, more than one clinician should, after all data have been collected, reweigh the evidence, and at Rochester this is the invariable rule. Thus, in 3 per cent. of the patients studied the consultant was able to elicit highly important facts from the history which had been completely overlooked by the first examiner. In over 3 per cent. valuable details in the physical examination were

noted by the consultant and were added to the evidence, and, finally, 4.1 per cent. of the final diagnoses, as made by the original examiner, were checked up and corrected by the consultant.

The patient with vague intra-abdominal symptoms, presenting himself for the first time, will require in the neighborhood of an hour for his first examination. Thus in the clinic where the studies forming the basis of this paper were made the examiner, working eight hours a day, will average between 7 and 9 cases. Let this number be increased to 12 or 14, and the diagnostic mistakes that would immediately appear as the result of the necessitated haste would at once be so apparent and humiliating as to cause an immediate reduction in the number of new cases daily investigated. Even with infinite care in the study, during an eight-hour day, of but 7 or 8 cases, significant data in the history and valuable details in the physical examination will be overlooked. An investigation of the latter question revealed that in making general physical examinations the commonest details missed ran as follows:

Small ovarian cysts and other pelvic masses.

Small adenomas of the thyroid.

Small hyperplastic thyroids in early hyperthyroidism.

Enlarged cervical, axillary, and other lymphatic glands.

Presystolic and other valvular murmurs.

Absent knee-jerks.

Thickened seminal vesicles.

Splenic enlargements.

Epigastric masses in carcinoma of the stomach.

High rectal metastases in carcinoma of the stomach.

Eye signs (in high tabes and other cord and cerebral lesions).

Sclerotic pallor suggesting the anemias.

Rectal and rectosigmoid masses in carcinoma of the rectum.

Finally, and probably the most dangerous, omissions result from the failure to recognize the direct indication for some special form of study in the case. Thus a serum test, a fluoroscopic examination, a pyelogram, or an examination with the proctoscope, may be all that is needed to at once brilliantly illuminate a hitherto obscure problem.

In moments of pessimism when, after the clinician has delved exhaustively in a case for days only to see the diagnosis of which he was sure proved at the operating table to be grossly wrong, is he apt to muse that, withal, the best diagnostician is but the cleverest guesser.

Even with the immeasurable assistance rendered us by the culture

tube, the roentgen ray, the blood count, and the serum reactions, the prime requisites to the making of a successful diagnostician are the same today as they were when the Crookes tube, the microscope, and the guinea-pig were unknown to medicine. And so is the ancient statement truer than ever that incorrect diagnoses are oftener made as the result of lack of care in the making of the examination than as a result of lack of knowledge of how that examination should be made.

REFERENCES

1. Rosenow, E. C.: "Elective Localization of Streptococci," Jour. Amer. Med. Assoc., 1915, lxv, 1687-1691.
2. Eusterman, G. B.: "Essential Factors in the Diagnosis of Chronic Gastric and Duodenal Ulcer," Jour. Amer. Med. Assoc., 1915, lxv, 1500-1503.
3. Cabot, H.: "Stone in the Kidney and Ureter: A Critical Review of 157 Cases," Jour. Amer. Med. Assoc., 1915, lxv, 1233-1234.
4. Braasch, W. F., and Moore, A. B.: "Stones in the Ureter," Jour. Amer. Med. Assoc., 1915, lxv, 1234-1237.
5. Walker, I. C., and Haller, D. A.: "Routine Wassermann Examinations of Four Thousand Hospital Patients," Jour. Amer. Med. Assoc., 1916, lxvi, 488-491.
6. Cabot, R. C.: Differential Diagnosis, Phila., Saunders, 1915, vol. ii, pp. 229-230.
7. Hall, G. W.: "Tabes and the Surgeon," Illinois Med. Jour., 1910, xviii, 527-533.
8. König: "Tabische Krisen," Deutsch. med. Wchnschr., 1911, xxxvii, 2357.
9. Lomnitz: "Gastrische Krisen als Frühsymptom der Tabes," Deutsche med. Wchnschr., 1910, xxxvi, 486. Quoted by Singer, K.: "Die Krisen der Tabiker," Berl. klin. Wchnschr., 1911, xlviii, 2168.
10. Charcot, J. M.: Lectures on Diseases of the Nervous System, London, New Sydenham Soc., 1881, p. 27.
11. Nuzum, J. W.: "Needless Surgical Operations from Failure to Recognize Tabes Dorsalis," Jour. Amer. Med. Assoc., 1916, lxvi, 482-485.

THE OMENTUM, ITS PHYSIOLOGIC VALUE AND
THE NEED OF ITS PRESERVATION *

CHARLES H. MAYO

The readiness with which the great omentum, either in part or in whole, is sacrificed in abdominal surgery, especially in colectomy, seems to call for an occasional word of appreciation of the value of this wonderful structure.

The omentum first appears in the lower vertebrates. It does not exist in fish nor in birds generally, but is found in birds of prey, undoubtedly as a protective organ, preventing by its soft pad the piercing of the intestines by spicules of bone in the food-remnants they contain. In man the great omentum is attached to the greater curvature of the stomach and hangs down as a fold over the intestines, the under side of the fold being attached to the transverse colon at a level nearly as high as the stomach. Occasionally the right fold may be attached to the gall-bladder. In some animals the attachment to the colon does not occur, as in the dog, cat, rabbit, and pig. Vesalius believed that the transverse colon is supported by the omentum as a ligament, and his influence still affects some surgeons, who hold that ptosis of the transverse colon is a disease condition and advise surgery not only for mechanical relief, but for the benefit of varied mental, nervous, and physical complaints.

De Renzi, and Boeri, Pirone, Crouse, and others believe the function of the omentum is somewhat like that of the spleen. In structure its peritoneal layers and cellular tissue with many vessels capable of great distention and storage of blood, numerous glands, and large lymph-channels embedded in and traversing its fatty structure, indicate that it is an organ of extensive absorbent capacity and probably absorbs more through the blood-stream than through the lymph-channels. The fat seems to be deposited quickly and is as quickly given off. Without it the omentum may be quite insignificant, and with it, often very large, weighing several pounds. When the lymph-channels are obstructed above the omentum, they are shown to be numerous and of great size. Tests which were made to eliminate the lymph-flow by tying the thoracic duct, and which were supposed to indicate that the bulk of absorption

is hemic, were considered imperfect or inconclusive in their results, as, according to Crouse,* the major part of the lymph return is to the right lymph-duct by the right lung and anterior mediastinal route.

Posture is not so potent a factor in the absorbing power of the omentum as formerly believed. The Talma-Morrison operation is of value in certain cases of ascitic accumulations within the abdomen, since it furnishes expansile drainage plugs; the peritoneum, being perforated from within out, by tags of omentum leads drainage to a rich absorbent area just outside of this encapsulating structure.

While the omentum does not have the power of automatic motion, it is so readily moved about by respiration, intestinal movement, and changing abdominal pressure, that it would almost seem to have a sense of adjustment. For this reason it is often found where wanted, attached to, or surrounding, by walling off, so to speak, infectious processes in the abdomen. It holds a high percentage of phagocytes of the defensive repair type, and, unlike other areas, does not require the presence of structural infection to slowly develop or gather the phagocytes. The omentum is always ready with its protective army. In time of need there is quick exudate of lymph and adhesions of omentum. Pirone and Heger show that with the loss of the omentum the main phagocytic power of the peritoneal cavity is lost.

Today the trend of opinion is that cancer is a manifestation of some form of infection; if this is so, the infection must be of a bacterial type, which is non-irritating to the omental cells. Adhesions of the omentum to cancer areas rarely occur unless there is a secondary infection or perforation or impending perforation. Once attached to cancerous areas in the presence of general abdominal carcinosis or carcinomatous fluids, the omentum rapidly succumbs to cancerous infiltration.

The omentum makes hernia manifest by its insinuating entrance into peritoneal pockets in the lower abdomen. Femoral hernia is undoubtedly due to the drawing out of peritoneum through the femoral ring by traction of attached preperitoneal fat. The omentum may not early reach to the opening or may not find the sac opening ready, but ultimately it becomes its first occupant. The same is true of those small peritoneal pouches along the cord structures in the male or the round ligament in the female—small potential hernias in which the omentum becomes the dilating agent.

Persons who have had abdominal operations and still have abdominal

* Crouse, H.: "The Omentum; its Embryology and Histology: its Physiological Uses," Bull. El Paso County, Texas, Med. Soc., 1915.

pain or later develop a new abdominal pain, nearly always are told that
they are suffering from adhesions due to the former operation. The
disease for which the operation was performed is often not considered.
So-called adhesions are not of infrequent occurrence; a goodly percentage
of people have them.   The peritoneum is a thin layer of cells not fitted
to repair like the skin with its several layers, and adhesions readily occur
from injury or infection; in fact, this is a factor of safety against perfora-
tion and infective damage and is constructive rather than destructive.
In cases in which secondary or tertiary operations for adhesions have
been performed and adhesions found to fat areas but none connecting
naturally movable structures to firmly fixed structures, the cause of the
symptoms will not be removed by separation of the adhesions.   In
such cases the surgical suggestion is made that further exploration is
indicated in order to determine the presence of real pathology or to
classify the condition properly as a neurosis requiring other lines of
treatment.

In abdominal surgery along constructive lines the omentum is won-
derfully useful.   Suturing it in position to protect against adhesions or
at least make them harmless; covering abraded surfaces and adjusting
omentum and fatty round ligaments by suture to keep the stomach or
duodenum away from the denuded surface when they are seen in con-
tact after cholecystectomy; wrapping the structure loosely around in-
jured surfaces of intestine or those areas of poor vitality or freshly united
bowel; fixing it by suture over perforations after their closure; covering
the large yellow plaques of cancers of the stomach which are found on
exploration to be inoperable yet not obstructed and which may blow
open with the distention of stasis following simple exploration, are all
very useful protective measures recommended by many surgeons.   Free
grafting of the omentum is a temporary patch which soon necroses and
becomes absorbed after serving its purpose.

Great scrotal hernias of the intestines or omentum as well as of the
umbilicus are often to be dealt with.   Several surgical principles are
involved.   The abdominal contents which protrude may be removed if
composed of only omentum or returned within the abdomen if composed
of intestine and omentum.   The return of a large mass may be dangerous.
When the mass has been extruded for a long time and has, in fact, almost
lost the right of habitation, the abdominal wall becomes adjusted to its
lessened contents.   In such instances large hernias cannot be returned
without increasing intra-abdominal tension and causing danger of ob-
structive stasis.

In all but emergency cases a week or ten days of preparation should be given; for example, daily physic, light diet, and, above all, no exercise but rather rest in bed to secure relaxation of the abdominal wall. The omentum rapidly loses its fat, and it may then be safely replaced with the intestines. In removing portions of omentum it should be pierced with forceps, and after crushing, ligated in sections.

To return to the original proposition of preserving the omentum whenever possible, at least not ruthlessly sacrificing it, we must speak of the operation of colectomy. In cases of operable cancer of the transverse colon the omentum must be freely removed. If it is involved by the disease, the operation will probably be palliative only. In some cases of colectomy we have found that the loss of the great omentum resulted in matting adhesions of the anterior layer of intestines, with free movement of intestines behind this layer—apparently a protective measure. Such cases have been frequently noted in reports of complications resulting from colectomy and are believed to be due to the loss of the protective influence of the omentum; that is, loss of warmth, fat, aid in peristalsis, and maintenance of local circulatory balance. Colectomy, however, is now so often advised and performed for stasis, toxemia, and various hitherto and still incurable maladies, that lifting up the omentum and separating it from its colonic attachment with a sharp knife, rather than sacrificing it, has been suggested by Lardennois and Okinczyc. The same separation is made by Pauchet to reach the posterior wall of the stomach, the omentum being left attached to the stomach and free from the colon, as it is in some of the lower animals. A few ligatures only are required to control hemorrhage.

In colectomy we have preserved the omentum and nearly all its blood supply by a long incision nearly the length of the transverse colon in the line of a longitudinal band. The incision is made through the peritoneum and muscle only. The mucosa readily peels out of its muscular bed by gauze dissection, leaving a few bleeding points, most of which are controlled by temporary gauze packs. At each side of the abdomen the longitudinal incision is converted into a circle around the bowel, the lateral colon on each side being wholly removed in the usual manner. The margins of the split outer wall of the colon are inverted into its raw surfaces and held by a few sutures. Right colectomy removes the greatest absorbent surface of mucosa, and while preserving the omentum, is as effective as a more extensive colectomy in the majority of cases of surgical stasis.

AN APPRECIATION OF THE ROENTGEN RAY AND A WARNING AS TO ITS USE IN SURGICAL DIAGNOSIS *

CHARLES H. MAYO

In this age of science medical progress has fully kept pace with other sciences. The most important discovery was the function of the single cell, and today the smallest element has become the subject of the greatest study. With the knowledge that microörganisms are the specific cause of disease, progress became rapid; in fact, almost a new medicine has been written along broader lines.

Within the activities of many of us marvelous discoveries have been made: In mechanics, the submarine, wireless telegraphy, and aviation; in medicine, among others, the roentgen ray and radium. The latter have been found to be of such aid in the treatment of disease that they constitute specialties in which many hundreds of physicians are now engaged.

When the main principles of a science are discovered, its progress is unceasing as our knowledge increases. From the old glass and mica-plate static battery we passed through the use of several forms of coils, until now machines and tubes, as well as methods, have become standardized. The roentgenologist knows almost exactly what to expect, the roentgen ray having opened the windows for the observation of new truths to prove or disprove the correctness of old theories.

Naturally, from the penetrating character of the ray, its first aid to medicine and surgery was in outlining the bony skeleton. It showed deformities and anomalies, and above all afforded perfect observation of fractures. The treatment of certain fractures has been almost revolutionized by early diagnosis and aid in adjustment, and surgeons have become convinced of the necessity of the open method of treatment in cases of failure of adjustment. At various ages the bones of the body

have a characteristic roentgen appearance. Because of this, diseases of the bones and joints, which cause deviations from the normal appearance, have become, as it were, an open book. However, with the roentgen picture came the danger of failure to interpret it properly. Many operations far too radical, such as amputation of limbs, have been advised in the belief that death from sarcoma would otherwise result, when as a matter of fact the disease was but bone cyst or cartilaginous tumor. The great value of the ray has been demonstrated to the surgeon also as a means of locating foreign bodies, such as needles, bullets, and glass in the tissues of the body or in the alimentary tract, indicating whether in such cases surgery is necessary, and when necessary, preventing overextensive dissection.

Further advance in the use of the roentgen ray as a diagnostic measure came in the roentgenoscopic and roentgenographic examination of the chest. The size of the heart and aorta is easily determined, and in diseases of the lungs, especially the early stages of tuberculosis, fibrosis, local bronchiectasis, and cavitations, the diagnosis is more sure and definite than by previous clinical methods. In diseases of the pleura with exudate, fistulas in general and cases of empyema especially, opaque solutions are injected to outline the size and shape of cavities. In this manner the value of Beck's paste in diagnosis and treatment was discovered. Especially important is the aid of the roentgen ray in the diagnosis of early metastatic carcinoma of the lung and bones. In these cases the roentgen findings prevent serious primary or secondary operations when the original lesion is in the mammary gland or thyroid. When such malignancy has existed for more than a year, there may be 14 per cent. of metastases to lung and bone. I believe that these structures should not be treated surgically when such metastatic growths are found and that other forms of treatment have greater influence in prolonging the life and comfort of the sufferers.

It is now possible to outline the whole alimentary tract from the esophagus to the anus by roentgenoscopy or the roentgenogram. Diverticula in the esophagus may have been previously diagnosed, but the ray shows when there are large sacs extending into the chest and indicates to the surgeon when a two-stage operation should be done to prevent danger of infecting the mediastinal space, a complication that is usually fatal. Also by means of the ray foreign bodies, strictures, and the dilatation accompanying cardiospasm are shown, all of which findings aid wonderfully in the diagnosis.

In diseases of the stomach the surgeon depends largely on the roentgen ray to identify and locate the niche of ulcer, hour-glass stomach, the location and operability of cancer of the stomach, contractions at the pylorus and foreign bodies; also to ascertain whether a palpable epigastric mass is intrinsic or extrinsic. Formerly, such conditions were often diagnosed as surgical lesions and a complete diagnosis was revealed only by exploration. Thus many persons suffering from inoperable carcinoma have been subjected to unnecessary operation, their vitality being thereby impaired without adequate benefit.

Probably no organ in the body is more often the seat of common complaint than the stomach, but, as W. J. Mayo says, "so frequently are those symptoms reflex that only one person in ten who complains of gastric trouble as the major symptom actually has disease of the stomach." In an extremely high percentage of cases duodenal ulcer is diagnosed by bulbar deformity, obstruction, and hyperperistalsis. Secondary manifestations in the stomach, such as spasm of the pylorus, hyperperistalsis, etc., often indicate infection of the gallbladder with or without adhesions. The complaint referred to this region is probably more exaggerated than that referred to any other region in the body, unless it is the female pelvis, and it has often a hypnotic influence. However, it is the examiner who receives the suggestion and is led to exaggerate the findings. The unfortunate surgeon failing to find the supposed lesion pleases neither the patient nor the diagnostician. It is to be deplored that so many suggestions coming from the profession are of disease rather than health.

The ray is useful more often in diseases of the colon than in those of the small intestine. In both intestines, however, tumors, chronic obstruction, dilatation, and stasis show remarkably well, and in a large majority of cases the roentgenologic findings can be depended on as a means of diagnosis.

The medical literature of the past few years has been filled with descriptions of colonic stasis, ptosis of the abdominal organs, and methods of operative relief. The stomach and colon being easily located in the roentgenogram readily show changes of position which are often supposed to be abnormal and have led to much inadvisable surgery. Those engaged in specialties occasionally fail to comprehend the association of general diseases, the habitus, the muscle tonus, the height, breadth, weight, and the influence of environment, and the narrowness of the

viewpoint of the specialist often accounts for the unwarranted operation recommended.

The surgeon is frequently confronted by patients who have been hypnotized by the suggestion of physicians into believing they have disease. These patients appear with a box of roentgenograms showing that their stomachs are low. Their physicians have recommended gastro-enterostomies or colectomies, although there is but slight, if any, delay in the emptying time. Such persons are usually women, though sometimes they are men, still worse subjects. They have weak muscles, are usually tall, narrow of girth and long of loin, and, therefore, it would be surprising to find that the longitudinal muscles of their colon were in proper tone. With but a few inches of lateral width in which to attach 24 inches of transverse colon, the latter naturally hangs lower. If stasis is present, these patients have been told that all their ills, mental and physical, will be relieved by elevating or shortening the colon, and the surgeon who refuses to operate is looked upon as an obstructionist.

In genito-urinary work the surgeon is appreciative of the great aid afforded by the x-ray in diseases of the ureter and kidney. The shape and capacity of the pelvis of the kidney, the location of stones in the kidney or ureter, as well as their number, are often shown. A knowledge of the presence of multiple stones is of the greatest importance as it is generally believed that recurrence of stone in the kidney occurs in 50 per cent. of the cases. In a series in our clinic of 450 cases of stone in the kidney operated on more than a year ago the actual percentage of recurrence was 9.9, but the number of multiple stones diagnosed and removed was high. Deformities of the pelvis of the kidney are outlined by the pyelogram, thus making possible early diagnosis and operation on hypernephroma.

Diseases of the gallbladder are the result of infections, specific types of streptococci having been brought to the base of the mucosa by the vascular stream. Gall-stones do not develop without previous inflammation of the gallbladder. Undoubtedly a great deal of effort has been wasted by the roentgenologist in endeavoring to diagnose gall-stones. To be sure, it can be done in a certain percentage of cases, but if even done correctly in 100 per cent.—and it is correct in scarcely half that number—the method avails nothing in the group of patients suffering from cholecystitis without stones, strawberry gallbladder, papillary gallbladder, and even early carcinoma patients, who make up more than one-third of the total number of those with disease of the gall-

bladder. To depend on the roentgen ray in these cases, except as a corroboration of the clinical diagnosis by indicating the probable presence of stones, would be to step back in the clinical progress of medicine at least twelve years.

In the present period of medical advance the chief subject under discussion is the focal origin of disease, both general and local. Very frequently foci of disease are carried by those suffering from chronic relapsing rheumatism, neuritis, myositis, etc. One of the most common sources of such infection are painless apical abscesses in the jaw, which empty into the circulation from time to time through the venous channels in the bone, each delivery constituting a new attack—a so-called relapse. In the search for such foci of infection the roentgen ray quite naturally supersedes all other means of examination.

What the surgeon most desires in his report from the roentgenologist is brevity, like that of pathologists' reports regarding diseased tissues. A detailed statement of the various types of cells and tissue-structures sent to a man who is not an expert fogs his mind and clouds the clinical evidence previously obtained. To stand well with the surgeon, the roentgenologist should be specific in his conclusions, avoid verbose descriptions of his findings, and when unable to make a diagnosis, frankly report the case as "indeterminate."

The modern roentgenogram may be accurate, but man is not infallible. The specialists making roentgen-ray examinations seldom have the opportunity to follow their patients to the operating table and visualize the abdominal contents directly. Moreover, they do not have the opportunity to correlate their findings with those of equally good men who are quite as anxious to show the importance of laboratory and clinical tests and well-taken histories. Only by such correlation can a normal, wholesome restraint be established and the greatest proficiency in clinical diagnosis be attained.

HOSPITAL PROBLEMS OF GONORRHEA AND SYPHILIS *

JOHN H. STOKES

Sexual disease is only just beginning to obtain recognition as a hospital problem. The scanty attention it has received has been due less to ignorance of its importance than to deliberate refusal to deal with it. Two recent estimates agree in showing that, excluding frank syphilis, about 6 per cent. of all patients undergoing treatment in a general hospital have positive Wassermanns. Another report mentions 16 per cent. positives in 500 cases. Only 2 per cent. of these were diagnosed clinically as syphilis. This is "incidental syphilis," so to speak. For syphilis frank and uncomplicated few hospitals profess to make any provision whatever. In 1914 it was estimated that the city of London, with a population of 7,000,000, had 163 beds actually available for the care of sexual diseases. The Sydenham Royal Commission has just found the same condition throughout Great Britain. Of 30 general hospitals in New York City, a recent investigation showed that only 10 receive recognized cases of syphilis in active stages. Nine receive adult cases of gonorrhea needing hospital attention, and 3 receive and treat active gonorrhea in little girls. Thirteen of 30 will not even receive medical cases with known syphilis or gonorrhea. Detroit until recently made no provision for hospitalizing active sexual disease, but has now developed two clinics. Chicago has the Cook County Hospital, the only open special service I know of in the city—200 beds to 2,000,000 people. The problem exists—it has simply been ignored. Pontopidan, on the basis of a large experience with the Danish system, estimates that one bed to 2000 of the population is insufficient for the adequate care of sexual diseases. How desperately we need a general survey to show us the extent to which we fall short even of this ideal can be imagined.

The problem of the hospitalization of sexual disease is interwoven

with the venereal stigma. The first effort in the development of hospital service for the sexual diseases must be directed at breaking up the venereal connotations and clearing up the confusion of medical and moral issues which has muddled our outlook. As a practical illustration, the customary association of syphilis and gonorrhea on a service seems to me to contribute little to the care of either, and to favor directly the perpetuation of the venereal stigma upon them both. Gonorrhea can be smuggled into the hospital under the cloak of genito-urinary surgery. and syphilis under that of diseases of the skin, since dermatologic opinion is so essential to the diagnosis of the disease during a large part of its course. Such an evasion side-steps a temporarily unmanageable public prejudice and ignorance, and allows us to proceed at once with practical measures while the slow work of reëducating sentiment is carried on.

Making sexual disease the province of the general, and not the special venereal, hospital is another form of the same method to break the force of the venereal stigma. This principle has been recognized most recently in the recommendations of the Sydenham Commission, and is now incorporated in the provision being made by the Local Government Boards of Great Britain for the care of these diseases. We would be retrogressing, I believe, if we subscribed to any other point of view in this country. Nothing will go farther to popularize good treatment than to make the recipient of it inconspicuous.

Speaking now directly about syphilis, with which I am more familiar. eight ways occur to me in which the general hospital can contribute to the management of the disease.

1. *A Study of the Entering Patient by a Serologist.*—A competent serologist in a hospital laboratory can detect the disease in 6 per cent. of the hospital population in whom it is more or less concealed. The routine Wassermann test on entering patients is then an ideal to be striven for. and will ultimately take its place with urinalysis and the estimation of blood-pressure as part of an adequate examination. Dark-field equipment should also be installed to aid in the quick diagnosis of acute cases, doubtful mucous recurrences, etc. Such recognition of entering syphilis is insurance for the staff, in whom, in general, house infection is too common and entirely avoidable.

2. *Prolonged Observation.*—Prolonged observation of a patient in a hospital under control is an asset in the care of any disease, and in none more than syphilis. The brilliance and éclat of even reasonably

effective therapy often lead one to slur over the valuable impressions as to the patient's resistance and reaction which have been gained by deliberate and painstaking observation of the case from day to day. The carefully made chart, the coöperative opinions of aurists, ophthalmologists, and internists based on continued study, have a special value in outlining prognosis and determining future treatment. The treatment of active hereditary syphilis was first recognized by Welander as the province of the school-hospital, an institution as yet unknown for this disease in this country. Lumbar puncture should also be a hospital procedure.

3. *Intensive Treatment.*—The most intensive treatment of syphilis, especially before the patient's tolerance and condition have been determined, is best carried out, in my opinion, not under ambulatory conditions, but in the hospital. This is especially true of the administration of salvarsan, the first injection of which may be followed by sharp reactions, even with graded doses, and later by imperative warnings of intolerance. Ambulatory technic for this treatment necessitates reductions in the later dosage and lengthening of the intervals. The clinician's control over his technic and procedure, sacrificed when the patient is allowed to go unobserved after the injection, is vital to long-run successful results and should, I believe, become a standard and universal feature of our practice.

Severe constitutional involvement in early syphilis is not uncommon and deserves hospital care. Even the milder grades of infection make striking gains under diet and rest, both of which are valuable adjuncts to specific treatment which the patient can seldom avail himself of outside of a hospital. The accidents of late syphilis in viscera and nervous system usually profit by and deserve hospitalization.

4. *Quarantine.*—As a contagious disease, syphilis in many cases needs hospitalization for temporary quarantine. Especially is this true of the irresponsible and ignorant, who should be compelled to accept it if necessary. Temporary sterilization by a single dose of salvarsan in the dispensary carries with it serious later risks of neuro-recurrences, and is hardly a substitute for the inhibitory effect, for example, of a series of three doses in six days, such as hospital control permits. Quarantine, deliberate study, massive treatment effects, these three alone justify and make imperative beds for all syphilitics in active stages of the disease.

5. *Social Aspects.*—I am fond of comparing the hospital service for

syphilis with the sanitarium for tuberculosis. It is essentially a sanctuary for many, and provides, moreover, a place and opportunity to reconstruct and rehabilitate the victims of one of the most peculiarly distressing of human ailments. Morale forms an important though often little appreciated factor in the course of the disease, and social responsibility must be made to reach a high plane in the victims of syphilis if those around them and society at large are to be protected from harm. In the comparative calm and sequestration of the hospital, separated for a short time from the bustle of affairs, and under the influence of far-sighted and humane physicians, impressions and suggestions can be made with greater hope of permanence than under average outside conditions, and more prolonged and effective coöperation for cure established and maintained.

6. *Treatment Control.*—I should like to urge, without excluding the dispensary from the field, the possibilities of the hospital clinic for syphilis as a center for treatment control. Haphazard and incidental care mars the whole modern scheme for the effective treatment and cure of the disease. A little treatment may be worse than none at all. Yet this is all the average patient gets. "Pillar to post" summarizes his fate. Of all things, he needs most one central governing power, always interested in his condition, always directing his course towards cure, always in full possession of the facts about his case. Patients seize upon this idea with avidity, and I am encouraged to attempt a practical scheme of the sort for the Rochester service. The prestige of a hospital, its disinterested character, the ample facilities for the development of the necessary record and follow-up system, all make it potentially an effective instrument for this sort of work.

7. *Coöperation.*—Those who work with syphilis in hospital and dispensary, trying to carry through modern methods of cure, realize that outside medical coöperation, when it must be used, too often proves a weak tool. Lack of coöperation, lack of the spirit of coöperation, lack of the common knowledge and methods which make coöperation possible, lie at the bottom of it. The patient gets pills when we know he needs rubs, or iodids when he should be saturated with mercury. The hospital service has it in its power to spread higher ideals of treatment, and to illustrate them to physicians who wish to coöperate with it in the care of its patients. It is not beyond reason for a clinic to maintain a register of physicians who have taken the trouble to visit it and ascertain its methods, and besides offering them valuable information,

regard them as a sort of coöperative outside staff, and refer patients to them for intelligent care. Such a reference list of men who will treat patients sent them by methods in harmony with those of the central bureau, and in coöperation with it as well, seems worth trying for, at least to one who has daily reason to appreciate the chaotic condition of syphilitic therapy among physicians in general practice.

8. *Facilities for Study.*—The service of the hospital to the cause of investigation and research is, I believe, unique and in no field more so than that of syphilis. The struggle to do effective, basic original work under the limitations of dispensary practice carries impossible odds. A shifting material, a hiatus between each two periods of observation, a line-up always pressing forward for more and more superficial attention, are no foundation for painstaking work. He is a hero who makes head against it. May the gods save us from the torrent of patients, the struggle with inadequate assistance, the sodden burial of our ideals under tons of routine. A service of even a few beds with a small laboratory and an organization that saves to its staff a few precious hours of leisure in which to mull over its patients, to know them, to sit on a stool and watch them, absorbed in thought, is a powerful force in the development of originality and may be the nurse of genius.

The practical problems of organization of a bed service must vary with local conditions, and cannot be detailed in advance. They differ widely from those of the dispensary. If there is an attending physician or if a clinician is invited to join the staff, the fewer his outside interests, the better. As in many other fields of medicine, the advent of the full-time man will be, I believe, an advance worth the cost. When the senior is not on full time, I would urge a permanent resident who should be a student of the disease, living in the midst of it, and having the *savoir faire* and qualities of heart and mind which enable him to appreciate it as a social and psychologic as well as a medical problem. Rotating service interns should study the disease only under his control and direction, and those with merely perfunctory attitudes of mind toward it should be carefully excluded.

A hospital-service for syphilis may be pay or free. As the state grows to larger appreciation of its responsibilities, we may perhaps look forward to the latter ideal, now embodied in the Scandinavian and Italian systems and foreshadowed for us in the action of the state of Michigan in its recent provisions for the care of sick children and adults. In the interregnum between *laissez faire* and this new ideal, however, there is

a place for the pay service for those of moderate means, who usually fall heavily between the two stools of high-priced specialism and the charity clinic. Such a pay hospital clinic, limiting its field, is under the necessity of protecting itself, on the one hand, from "dead-beats," and on the other, from dissatisfied and unmanageable wealth. The require- ment that a reasonable fraction of the fee, especially for salvarsan, be deposited in advance, disposes of many of the former and is a proper feature of the business management, provided it be administered with such discretion that special distress and worthiness can have help occasionally.

The mechanics of operating a service in a hospital involve complexi- ties that do not appear on the surface and are more or less *sui generis*. The necessary protection of the incognito of the better and more sensi- tive types of patients flatly precludes herding or labeling methods. Venereal wards are as unsocial and unintelligent a provision for syphilis as a venereal hospital would be, and make hospital care a luxury limited to "down-and-outs." Self-respecting people will not avail themselves of it. The private room is the nearest approach to the ideal. On my service at Rochester I hope to develop this sort of care to a fine point, and thus far I have found it makes an appeal. The suppression of gossip, careful guarding of correspondence, and protection of the records are all necessary. Prying eyes must be kept out. Privacy in treatment must be provided, doing away with salvarsan line-ups, etc., and the ut- most care taken that when patients are thrown together innocently infected and unsophisticated persons are not brought under the influence of black sheep. If isolation wards are used, it is a constant struggle to keep them from being stigmatized by gossip. Attention to these de- tails makes the advantages of in-patient care, continuous or inter- mittent, available to all who deserve protection and consideration.

As a contagious disease, syphilis is, of course, a problem only in the primary and secondary stages. Even at its worst, its infectivity in the hospital is scarcely comparable to that of tuberculosis or even typhoid since the organism has an extremely low vitality. In the hospital dan- gerous syphilis is unrecognized syphilis, and against it the routine Was- sermann and the service for the disease are valuable protection. Pa- tients with active syphilis should stay in their rooms until salvarsan has been given. Their dishes should be phenolized or boiled. A "precau- tions" routine that I devised for the use of nurses describes the calomel prophylaxis provided in the medicine rooms in case of possible accidental

inoculation, the dangers of the pricked glove, the immersion of ther-
mometers, disinfection of instruments, and the buccal and anogenital
lesions of the disease, with the risks involved in approaching them.
Panic and syphilophobia in medical staff and nurses are occasionally
ludicrous and sometimes exasperating, but controllable by a little tact
and common sense.

Records, follow-up, and outside medical coöperation should be in-
tegral parts of one another, and between the three it ought to be possible
in the ideal system, to obtain for any one case a complete panoramic
picture of the disease from incidence to cure. Included in the record
should be notes describing the character of the coöperation of both pa-
tient and outside physician. A generation of such records would be a
priceless picture of the treatment of the disease in modern times, and an
authentic and convincing basis for legislation looking to its social con-
trol. As a practical skeleton for such a system I have been interested
in that in use for surgical cases in the Presbyterian Hospital, New York.
The importance of social service and visiting nurses, especially in con-
nection with familial syphilis, is easily appreciated.

Interdepartmental coöperation within the hospital is vital to the
efficiency of a service for syphilis. The holding back of syphilitic cases
by other clinics, on the one hand, or the failure of the department for
syphilis to extend ready coöperation outside of its own wards, on the
other, impairs efficiency. The creation of the department by voluntary
act of the hospital staff, and unhesitating and complete transfer to it
of all the responsibility for the care of syphilis are the sine qua non, and
without it men of high-caliber will not find it worth while to give the
service their attention. On the other hand, the clinician in charge of
the work should not lose sight of the wide clinical bearings of the disease,
and should maintain the interest of his colleagues in the progress of their
cases under his care as well as in the diagnosis.

My experience with gonorrhea has been largely indirect, and I look
to the discussion to contribute interesting details. I have found that
it can be handled satisfactorily by the department of genito-urinary
surgery among adults in a general service, or as a complication of syphilis.
In hospitals for children and lying-in hospitals, it is a dangerous con-
tagious disease, and should be managed with the rigidity observed for
diphtheria. I recall an epidemic in a children's ward traced by inference
to the visits of infected patients from a nearby maternity home. There
is nothing more distressing than the way in which a pediatrician may wake

up some morning to find half a dozen little girls on some seemingly well-managed ward ruined for life by gonorrheal vulvovaginitis. A large hospital, adhering to the venereal classification, placed some heredo-syphilitic children in a ward in which there were cases of gonorrheal vulvovaginitis, in spite of the protests of the pediatrician, and calmly permitted the little syphilitic girls to add the vulvovaginitis to their woes. The arthritic complications of gonorrhea seem to me to be legitimately within the province of genito-urinary work, since prostatic manipulations, etc., may well be part of the treatment, and these demand special knowledge of the genito-urinary tract. The follow-up on gonorrhea is fully as essential as that on syphilis, and might well follow the same lines.

The problems of gonorrhea and syphilis are not to be handled by any one agency to the exclusion of all others. Each one has its place, and each its problems with which it must perforce deal. It is no more possible to rate such diseases exclusively as hospital problems than it is to regard them solely as dispensary problems. Only in proportion to its ability to fill its place in a coöperative scheme will the hospital find its greatest usefulness.

I have touched elsewhere* on the value of the hospital in the study of gonorrhea and syphilis as diseases, not only of the physical body, but of the social *milieu* in which we move. The effort to understand and get back to first causes in the ideals, the daily life, and the mental outlook of the victims of these diseases, is a basic part of a public health movement against them. The opportunities offered by the hospital for intimate personal contact can create in this field a new type of physician to succeed the old family doctor—a physician who, though a specially trained clinician, has not lost by that fact the insight into the fundamentals of human nature which marks the student of life as well as the student of medicine. The studies of men trained to such an outlook in this field will, I believe, contribute much to the prevention of "half-baked" and premature legislation. Moreover, they will be a factor in the positive and constructive, rather than the merely negative and prohibitive, point of view which must dominate any successful campaign.

* Stokes, J. H.: "The In-patient Hospital in the Control and Study of Syphilis," Social Hygiene, 1916, ii, 207–231.

THE VALUE OF PUBLIC HEALTH SERVICE *

CHARLES H. MAYO

Man as a type is comparatively young, and it is but a few thousand years since language, organization, and breeding selection have developed the modern man from the primitive type. In the study of ancient medicine, skulls from two thousand to six thousand years old have been found which show evidence of dentistry by their filled teeth and evidence of surgery by their trephine openings. In his infancy man is the most helpless form of all young and requires the greatest care and protection. Since injury, sickness, and death have been his expectancy from the earliest period of history, medicine is naturally the oldest of all professions. However, for centuries the science was dormant, not from the ignorance of the medical men themselves but from the lack of general knowledge on the part of the people, and superstition associated with religion.

Medicine has made its most marvelous advance during the last century, and this progress came from a study of the cell as a unit in health and disease. The cell is the basis of plant and animal life. The condition of the single cell in health having been studied by means of the high-power microscope, its various changes in disease are now readily appreciated. The only life in the world, when life first began, was the single-celled organism, the bacterium or microbe. Death entered the world only when larger living forms appeared which were made up of aggregations of definite cell types having different and definite activities. All multicellular organisms, plant or animal, go through a process of birth or germination, growth, maturity, decay, and death. Single-celled organisms still exist and act as chemical solvents of organic and inorganic matter. Without such organisms there could be no plant life, and without plant life animal life would not be possible.

It was but a few years ago that anything relating to public health

work, state or local, was regarded by many as of little use, an added burden of taxation to the people and an infringement on personal liberty. Today the work of the public health service in preventing and eradicating contagious and infectious diseases is widely recognized and appreciated. In fact, those best informed, and especially those engaged in the care of disease, the members of the American medical profession, are advocating strongly the establishment of a Department of Health under the supervision of a member of the President's cabinet.

Next to its establishment and the enforcement of its laws nothing is of greater importance to a government than the maintenance of the health of its people. Health has come to be generally recognized as an economic principle. Some countries maintain compulsory workingmen's laws, protecting the people by state accident indemnity and old-age insurance. England furnishes free medical attendance to the fairly well-to-do as a national economic feature of her government. In this country also various insurance and accident compensation laws have been put into effect. Within but a few years, through the efforts of the public health service and the lecturers sent out by the American Medical Association, the people of the United States have become fairly well informed as to the possibilities of preventing disease. The value of medical examination of school children has been recognized and put into effect in nearly all cities. As a result of the propaganda of education concerning cancer this disease is apparently on the decrease, as many tumors are now removed before cancerous degeneration occurs. Tuberculosis also is no longer the scourge of thirty years ago. As a result of knowledge of the cause of yellow fever and malaria, a mosquito-bar has become its quarantine instead of the shotgun and the burning of cars resorted to a few decades ago. Body cleanliness and the destruction of rodents, the intermediate hosts of the disease, are the means of preventing typhus and the plague. Vaccination against smallpox has been practised so long that in this country its enforcement has become lax, and smallpox has not been stamped out here as it should be and has been by the paternal governments of Europe. However, the disease has been greatly mitigated as a result of preventive work and protection by immunization. Thus the world has been nearly freed of the great contagious diseases of the past which decimated mankind and struck fear to the hearts of the people.

The present war has greatly advanced medicine through the use of vaccines and serums in the prevention of disease where men are con-

gregated in great numbers.   In fact, it is because of the prevention of gangrene and infections and control of preventable diseases that the continuance of the present war is possible, the majority of those injured being able to return to the front, some of them several times.   In the wars of the past, eight men died of disease to every one who died of injury.   The compulsory use of vaccines and serums inaugurated on a large scale as preventive measures by the nations at war will place the future use of such treatment on a firm foundation.

The medical profession of the United States is very proud of the part its members have played in the advancement of the medical knowledge of the world to its present high standard.   In no country has this advance been so marvelous as in our own.   Our physicians it was who freed the pestilential Panama zone of disease in order that the Panama Canal might be built.   Intelligent communities are now demanding as their rights pure water and food and protection against contagious diseases. Citizens have even brought suit against municipalities because of disease contracted from infected water supplies.

People in America naturally tend to commercialism, and in a nation of this kind it is difficult to advance methods which in any way interfere with business.   Commercialism, therefore, greatly hampers the work of local public health officers.   The State of Minnesota, which finds it easy to raise about nine cents per capita for the care and prevention of disease in hogs and cattle, has an appropriation for health work of but three cents per capita.   Even with this small amount, however, Minnesota stands fourth in the public health statistics of the United States.   In many States the appropriation varies from a quarter of a cent to a cent per capita.

The legal value of a human life is commonly placed at $5000.   There is hardly a community in which an acting health officer, in the course of a year, would not be able to save at least one human life.   Accordingly, cities with a population of 2000 and up should have a whole-time health officer whose compensation should be at least the value of one human life. Such an officer should be modern in his views, fully equipped and trained in public health service.

NATURE, VALUE, AND NECESSITY OF TEAM-WORK IN A HOSPITAL *

CHARLES H. MAYO

The present program has exemplified the thought that the spirit of the age is best expressed in organization, and indicates the gradual approach to a rational socialism.

The history of hospital development takes the student back to centuries before the Christian era. After this period the idea became greatly broadened, although it was not until about 1500 A. D. that the true usefulness of hospitals was recognized.

HOSPITAL STANDARDIZATION.—The necessity for hospital standardization has been discussed in various medical meetings for several years, with the annual appointment of committees for reports, and much good has been accomplished from the publicity. The American College of Surgeons has, of necessity, taken up the work of standardizing hospitals, and all institutions which desire to be recognized must come within stated requirements. Such investigation and classification of hospitals will require several years. The greatest help is expected from this association of Catholic hospitals now holding its second annual meeting.

HOSPITAL LOCATION.—Hospitals in Europe have been more wisely located than in America, having a setting in spacious grounds, where they secure the full benefit of air, quiet, and sunlight. In this country we have built in the most congested areas, lacking every hospital need except plenty of the poor. In such localities there should be only emergency institutions or automobile ambulance stations. Hospitals situated in cities should have at least a country convalescent home, where ambulatory patients may recover. Automobile transportation of the sick is now so comfortable and rapid that distance is no longer a factor to be considered in the location of hospitals. ·

In modern times hospitals are quite dependent on their corps of

nurses, whose ability, training, and attitude toward the work are essential for efficiency. In Europe the social standard of nurses was for a long time very low. They were recruited from the lower classes, even from prisons. Fortunately, in America the profession of nursing was started on a higher plane, and our nurses excel those of the world in intelligence, education, and culture. In Europe the nursing profession was modernized and reorganized in the middle of the last century through the necessities of war, and the present war is rapidly improving the standard of hospital attendants in the countries involved.

A nurse's training is a liberal education in itself. The instruction in cleanliness, the knowledge and treatment of disease, and especially the instruction in preventive medicine and domestic science, are valuable not only to the family, but also to the community. Thus it is that the ranks of nurses are largely depleted by matrimony. A training school for nurses is essential at least for all large hospitals.

Efficient trained sister nurses are of great value in general nursing. They are permanent general supervisors over the nurses in the training school, and have a personal interest in maintaining the hospital standard.

The interns are a recognized factor in hospital organization. They are the physicians and surgeons in charge, representing their chiefs of staff. The intern is guided in the care of the patient, and the theory of his training becomes transformed into actual practice. Minnesota does not grant a diploma to a graduate in medicine until he has had one year of service in a hospital as intern following a four-year medical course. Further, the medical department of the University of Minnesota will not accept a student who does not hold an academic degree. When we have added to this a four-year medical course and three additional years of graduate work for a master's degree, the training of such an American physician is equal to, or better than, the requirements of any of the countries of Europe.

An efficient, harmonious working corps of physicians is very necessary in the organization of a hospital. It is not for us to discuss the method by which the staff of medical attendants should be chosen. They should certainly be considered for their fitness, and should hold their place on civil service if their efficiency is maintained. It should not be necessary for the hospital to furnish reputation for attendants who are below par and who have secured appointment by political or church pull, or the fact that they were family physicians of some of the directors. There are certain positions in a hospital which, to secure

the highest efficiency, should be maintained by fixed salaries—those of the pathologist, bacteriologist, chief anesthetist, and the surgical registrar. With the recognition of the fact that many of the acute and chronic diseases, local and general, arise from a local focus—the most common source being the mouth—the true importance of dentistry is now recognized, and a dentist should be associated with every clinic and hospital, or subject to consultation call.

HOSPITAL REPORTS AND RECORDS.—In the standardization of hospitals, efficient methods of making and keeping records of all sorts will be necessary, especially the records concerning patients, their care, and the results of operation or treatment. . . . The hospital authorities should keep a duplicate record of the character of operations and their results as well as the results of other treatment. This would make it possible on their own record to eliminate from the staff men who perform operations of questionable character. Necropsy records are most necessary, but, while they may be secured in a high percentage of cases if desired, too often are not wanted. Such records would standardize physicians.

With all the various hospitals, general and special, there is still need for one more—a hospital for diagnosis. In the rapid advance of medicine during the last fifty years we have seen the disappearance of that former friend and counselor, the family physician. Medicine has become so vast, so monumental, that it is no longer possible for one man to encompass it, at least in practice, although he may have very wide knowledge of the principles and theories. Team-work as exemplified in large clinics and in hospitals has become necessary in the care of the rare and complicated cases representing 10 per cent. of the total, while even special examinations for the well-known diseases require experts in various lines in order that the diagnosis may be proved and complications not overlooked. In the past such examinations could be secured by the wealthy, who could pay for them, and by the poor, to whom they were free. It is the middle class, the larger number, who are most dependent on the ability of one man or his assistant. The middle class in cities are frequently seen at free dispensaries because of the presence of specialists and more complete equipment. . . . The situation must be recognized and dealt with. To maintain a high standard and keep the profession filled with educated and cultured men who are equipped with modern apparatus, it must be made better. In order to do this,

it is necessary that physicians obtain more than the present average compensation. There are now less than half as many students of medicine as there were five years ago.

In large cities and in the medical departments of universities diagnosis hospitals should be founded solely for the purpose of observing patients, the making of all kinds of special examinations, including laboratory tests, special vaccines, and x-ray examinations. To be highly efficient, it should have also an experimental department. When the diagnosis has been completed, patients could be referred to their home physician with the diagnosis and the plan of treatment. From the librarian of the clinic could be sent references to recent literature on the subject. Some cases would be referred to special hospitals and sanatoriums, and others to surgical institutions. Such a diagnosis hospital would have the greatest educational value, and its main supporters would be the general practitioners, especially those located in smaller communities. Undoubtedly it would do much toward the elimination of that nefarious practice—the division of fees and the barter and sale of sick human beings.

DENTAL RESEARCH, ITS PLACE IN PREVENTIVE MEDICINE *

CHARLES H. MAYO

The dental profession, as such, and the medical profession are too widely separated. It is much more important that the dentist should know something of medicine than that the ophthalmologist and the otologist, as specialists, should know what they know of medicine. The latter are dealing with small areas of the body not nearly so important from the standpoint of disease as that for which the dentist is responsible. I believe that in the future all must take the same studies, the same final examination, and that all must go to the same institutions of learning, up to the point where the diverging lines of study of the specialist must be undertaken. I believe also that in the future the dentist must be taken into the great American Medical Association, as a part of that body. It is going to be necessary.

As we see things today it means there will be far less surgery and less sickness when the full benefit of the knowledge of modern dentistry and the cause of many diseases become known throughout the world. There should be four times as many dentists as there are today, and yet there is not room for more until they have educated the public to the necessity of their work. No matter how far advanced surgeons or medical men or men in any line of endeavor may be in a community, they know they could not have done their work unless the people of that community had been educated to the necessity for such work and the benefits they would derive from it.

Therefore, it is up to you dentists to institute an educational propaganda such as has been going out from the American Medical Association. You all know of its work during the past few years. It has distributed men throughout the country who are educating the public as regards the necessity for early examination and treatment for

cancer, in order that something may be done to obtain such cases for treatment during the curable stage of the disease. Educational measures of this kind should be undertaken in all branches of medicine which deal with public health.

The average duration of human life has been increased many years during the last half century, and this has come about more through the protection of the people by public health laws and the saving of children than it did through the knowledge of the use of drugs.

The next great advance in the prevention of disease, and that wherein dentists are so much interested, is the knowledge that chronic diseases, acute diseases, and special local diseases, i. e., neuritis, sciatica, and acute paralysis, come from mouth infections in the majority of instances; also that appendicitis, diseases of the gallbladder, and ulcerated stomach are caused by bacterial infarcts in the capillary circulation at the base of the mucous cells in these organs, and result in the same manner from local infections. While there are several sources in the body for the entrance of bacteria and their culture in a local focus, the mouth is far the most common situation. The tonsils very commonly harbor disease germs. We find these germs in pyorrhea in cavities and abscesses at the roots of teeth from natural decay and in apical abscesses, all of which are too often the result of bad dentistry. Bacteria, as has been noted, seem to be created by environment or developed for specific purposes, and bacteria cultured from certain disease regions of the body seem to have almost a specific selection for similar regions in animals when injected into their blood; thus appendicitis, gallbladder disease, including stone, and ulcer of the stomach can be reproduced as well as diseases of the nerves which are caused by infection. As before stated, these bacteria may be changed by environment and culture into different but similar strains having somewhat different activities. On the other hand, the germ of measles produces measles, the scarlet fever germ produces scarlet fever. Typhoid, small-pox, and all the known contagious diseases reproduce a definite specific disease.

Rosenow has been able to produce, with bacteria cultured from diseased teeth in man, similar diseases of teeth in animals; the proportion is small, as these animals are more resistant to such infections. It must not be understood that the specificity of bacterial selection of location only occurs, but that there are side-lines of development in other organs and tissues. There would be a few cases of rheumatism and a few cases of infarction of the kidney, a few instances of myocardial in-

'16—61

flammation and similar conditions throughout the body, but the main result of the experiment is to locate the disease in a similar region from that which the culture was taken, when cultured from secondary foci of disease. Those persons who have chronic local disease and also a septic focus about teeth or tonsils may often have the specific location of the primary focus proved by experimental work in animals, and be cured of the local infection.

GRADUATE WORK IN OPHTHALMOLOGY AND OTOLARYNGOLOGY

CARL FISHER

— — — —

Most disagreements as to the character of work to be demanded of
the graduate student, a candidate for a higher degree in medicine, hinge
on whether what is known as research or what is known as "practical
skill" shall be made the criterion of excellence. The problem is simpli-
fied for the present in the fields of ophthalmology and otolaryngology
by the fact that the graduate in medicine is not equipped with any
knowledge of these subjects worthy of consideration if he is to enter
these fields seriously. Furthermore, it is not desirable that the under-
graduate should have devoted himself to too specialized a course. His
training should prepare him in such a way that at graduation he may
choose any of the various medical careers which may fit most accurately
with his peculiar talents and tastes. Accordingly, the special student in
these branches must go through a definite course of didactic instruction
and "practical" experience. Heretofore this has been obtained, even
if in an incomplete and haphazard manner, only through internship in
eye and ear hospitals.

The question then arises: "When shall he start training for his
specialty?" There is little doubt but that the answer must be: "As
soon as he has finished the general hospital service required by this
State." I believe that with the growth in popularity of the associative
method of practising medicine we will eventually have our potential
ophthalmologists and otologists going directly into eye and ear hospitals
instead of general hospitals; on leaving the medical school. I have seen
much of men who have done this and also of men who have followed the
old (and vicious) dictum "ten years of practice first," and I am sure that
the advantage is greatly with those who have taken up the study of the
specialty early. Early knowledge of a specialty is like early knowledge
of a language; the ophthalmologist must use the precious acquisitive
years so that he shall not speak his language like one who picks it up

in the tired years. The question has next been proposed: "What studies shall have been pursued in the undergraduate course in preparation for these specialties?" Without committing himself to a specialty and without prejudice to his breadth of culture, the student who thinks he may take up ophthalmology or otolaryngology may very well lay emphasis on certain special courses. For both the ophthalmologist and otolaryngologist an exhaustive course in the regional anatomy of the head and neck (including the brain) would be invaluable. The ophthalmologist should also emphasize neurology and syphilis. A good training in these subjects might well be recognized in the graduate school and the extra time given to various works of supererogation, such as clinical trips.

I have said that there is a definite amount of didactic and practical instruction which may not be dispensed with, even for the sake of productive work. The requirements for such a course in ophthalmology have been laid down by the joint committees of the American Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology, and the section of the American Medical Association, which is ideal, according to present standards. This may be said to represent the crystallized opinion of the best minds we have. Without going into details (for this report may be consulted), suffice it to say that the course covers two years, during which time the student will have had comprehensive instruction in fundamental studies and practical experience with ophthalmic patients, will have dissected cadavers and operated on animals, and will have worked in the pathologic and physical laboratories. The course as outlined also provides for the writing and defense of a thesis on some subject in the broad field of ophthalmology and examinations on fundamental courses. This two years' course is intended to lead to a degree.

In otolaryngology we have no such clear-cut plan to go by. The American Laryngological, Otological, and Rhinological Society has formulated a plan, but the "ten year" shibboleth evidently prevailed in their councils. The technical requirements of this branch are certainly no more exacting than, if indeed as exacting as, those of ophthalmology. Two years should suffice for systematic instruction as in the older science. The recommendation of this committee, except in its requirement for a too prolonged course, is admirable and should be consulted by any one interested in this subject.   •

Under the conditions now prevailing in all but the oldest centers it

is customary for the ophthalmologist to constitute himself also an oto-laryngologist or vice versa. While this does not make for the deepest scholarship, it is consistent with entirely adequate treatment of pa-tients, and provision should be made for men who wish to practise both branches. It would seem to me improper for such men to expect to take a degree in both branches. However, a combined course in the two branches might properly be given, covering three years. This is possible because of the community of certain subjects to both branches, for example, rhinology, anatomy of the head, brain and neck pathology.

At conclusion of the two years' course in ophthalmology or otolaryn-gology the student should be granted a degree, for the public has a right to some sign whereby it may know that our man is not an "optometrist" nor a "six-weeks' specialist" nor a physician who does a little eye and ear work on the side. It also does not seem fitting that the degree of Doctor of Science, which in this university represents three years of work after graduation and the proved ability to discover new facts and relations, should be granted for purely receptive work. Accordingly, to the writer it seems better that an inferior degree be granted at this point (two years), such as Master of Arts in ophthalmology or in otolaryngology.

Is then productive work to count for nothing in the training of the specialist? The answer should be that men who show the ability to do this work should be encouraged to the top of their bent, after they have had a groundwork on which to build. The belief that only a few men have the temperament and the type of mind fitted for serious research is very widely held. It is a great mistake to think that the executive, so-called practical man, is at all inferior to the man of research; after all, this is the kind of physician to whom the teeming populace must look for healing. He is merely different—such a man will solace himself for not possessing the degree of Doctor of Science by the golden ducats which he accumulates, but he should not be forced to annoy the long-suffering profession with feeble laboratory investigations, which usually serve only to pile up more "things that ain't so" in the path of the seeker after new truth. Such a man will write useful clinical papers and valu-able reviews of the literature.

Granted then that our candidate has shown by his thesis at the end of his two years' course that he has the bent and ability for productive work, let him go on with it and complete his three years and be re-warded with his doctor's degree, as in other departments of university work.

Fortunately, the impulse to productive work is so strong in the proper investigator that, given any opportunity, he will throw his cap over the mill and embrace the scientific career unless the inexorable need to earn a living consumes all his time in routine work. It is the function of the university to provide this opportunity and to give achievement its due recognition.

This paper has purposely been kept to generalities, for until these general considerations have been decided, the details of courses of study are irrelevant. In closing, I will repeat that I believe that this systematic training in clinical and theoretic ophthalmology and otolaryngology which will receive the recognition of a degree in other places should be given such recognition by the University of Minnesota, as a matter of justice to the public and profession at large. The degree of Doctor of Science is intended to stand for proved ability to advance the science, and this degree ought not to be (I shall not say, lowered) changed to represent the bread-and-butter class of work.

THE STATUS OF THE GRADUATE DEGREE IN MEDICINE *

LOUIS B. WILSON

The University of Minnesota is offering graduate work in the various fields of medicine and surgery in three-year courses open to students who already possess the bachelor's degree, or its equivalent, the doctor's degree in medicine from a Class "A" medical school, and who have had at least one year's internship in a general hospital or a year's service in an approved laboratory of the medical sciences. On the satisfactory completion of such a three-year course the student is eligible for the degree of Doctor of Science in internal medicine, in surgery, in pathology, or in whatsoever other branch of medicine he may have chosen his major subject.

The status of this new degree of Doctor of Science in a medical specialty has not yet been determined; hence the following analysis and discussion. Since the conditions laid down regarding admission, residence, language requirements, thesis, and examinations are those which have long been applied by graduate schools of universities in the approval of candidates for the degree of Doctor of Philosophy or Doctor of Science, it has been assumed by some that the new degree in medicine scholastically reaches only the level of these older degrees. This assumption would seem to be incorrect, first, because of the longer time required to obtain the degree, and, second, because of the scientific ability exhibited by men with only the formal schooling represented by the doctorate in medicine or the baccalaureate in arts or sciences.

In the following diagram is shown the relationship in point of time required for the attainment of the M.D. degree in schools with the "Minnesota standard" and the attainment of the Ph.D. degree in universities in general, as well as the additional time required for the attainment of the new degree of Doctor of Science in a medical specialty.

It will be noted from the above diagram that four students, A, B, C, and D, who have had the necessary high school or other preparatory training, enter the college of literature, science, and the arts of the University at the same time and pursue regularly prescribed courses. At the end of two years in college, during which time he has taken a preponderance of prescribed physical, chemical, and biologic studies, A transfers to the medical school, and takes therein two years' more work, at the end of which time—a total period of four years—he receives his B. S. degree. B, taking a preponderance of prescribed physical, chemical, and biologic sciences, at the end of four years, all spent in the college, also receives his B. S. degree. C, entering the same college, but in addition to the required physical, chemical, and biologic sciences, adding thereto the special study of literature and the arts, at the end of three years in the college transfers to the medical school and in one year more, or after a total period of four years, receives his A. B. degree. D, entering the college and not indulging in a preponderance of the physical, chemical, and biologic sciences, but giving special attention to literature and the arts, receives his A. B. degree at the end of four years. Thus, each receives a bachelor's degree at the end of four years. If all four continue in the schools in which they were working at the time they received their bachelor's degree, B and D will receive their master's degrees at the end of another year and their doctorate degrees in science and philosophy respectively at the end of three years. Simi-

larly A and C, after two and three more years respectively in the medical school and one year in an approved hospital or laboratory, will receive their doctor's degrees in medicine. Therefore, at the end of seven years in the cases of A, B, and D, and of eight years in the case of C, all four have attained the doctorate degree. It would appear that men starting on the new three-year graduate courses in medicine offered by the University of Minnesota in the clinics and laboratories in the Medical School in Minneapolis and in the Mayo Foundation in Rochester, already have spent as much time in making their approach to the study of medical specialties as that required for obtaining the Ph.D. or D.Sc. degree in good institutions.

It is improbable that the native ability, the preparatory school instruction, the habits of study, or the skill of their university instructors, in the long run, is either better or worse in the group of doctors of medicine than in that of doctors of philosophy or science. Yet all will agree that, broadly speaking, there is a difference in the scientific attitude and habits of thought in the men of the three groups. This difference is best explained by the fact that of the four students whose scholastic careers have been diagrammed B and D have usually placed most intensive study on a very small field of science or art, while A and C have given less intensive study to a relatively much broader field. Incidentally, also, A and C are apt to have come more closely in contact with living conditions, with science in the making, as it were, than have B and D. The question is open to discussion whether B and D may not have concentrated too early and may not later suffer from lack of a broad knowledge of the science in the narrow field in which they have specialized and of other sciences related thereto. Some of the possibilities in this respect are pointed out by Stephen Leacock in one of his delightful "Essays and Literary Studies." Be this as it may, certainly A and C at least should be well able to see the broader relationship of narrow lines of scientific investigation. The question of present concern, however, is not the breadth of their culture,— which, unfortunately, is usually all too narrow to enable them to get the most real enjoyment out of life,—but rather the amount of their scientific ability, i. e., their ability to utilize in new ways old scientific truths and to discover, as well as to utilize, new scientific truths.

The estimation of the relative scientific ability of members of the various groups is very difficult. Even if we could measure accurately

each individual's scientific accomplishments, we still might be in the dark concerning his native ability or the amount of his premedical and graduate study not represented by formal schooling. But in comparing large groups these factors may fairly be assumed approximately to cancel each other.

Turning then to the question in hand—namely, the relative scientific ability of men who have ended their schooling with the attainment of the M.D. degree as compared with those who have obtained the Ph.D. degree, we may, I think, start with the premise that medical science in America has, at least, kept abreast with any other science during the last quarter of a century. We might, indeed, be within the truth in saying that it has led in development, but for the purpose of the present essay it is but necessary to assume that it has been equal to any other. The second premise, which we may lay down without question, is that the progress in medical sciences has been made by the men who are in the medical profession. It may further be postulated that in the United States most of the men who are responsible for the progress of medical science are members of the various medical societies whose membership is limited to those who have attained some distinction in some special field of medicine. It is presumable that there are instances of general practitioners who are not members of any society of the kind herein analyzed, and who yet have added materially not only to the practice, but also to the science, of medicine. Such individuals, however, must be so few that their omission would have relatively little to do with the figures or the question in hand. I have, therefore, taken the membership lists of the various medical specialists' societies in the United States of which the data were obtainable and have analyzed the scholastic attainments of the members as a matter of comparison. Elimination of duplicate membership has not been attempted, since it would have been both difficult and unfair.

The results of the analysis of the scholastic degrees of certain clinical medical societies of limited membership are shown in Table 1.

Membership in these clinical medical societies presupposes the possession of the M.D. degree. It is interesting to note that, taken as a whole, 56 per cent. of the 861 members have the M.D. degree only, while 44 per cent. have the M.D. with some other earned degree. It is also interesting to note that only 2 per cent. of the 861 members have the Ph.D. degree in addition to the M.D. degree.

TABLE 1.—ANALYSIS OF SCHOLASTIC DEGREES OF MEMBERS OF CERTAIN CLINICAL MEDICAL SOCIETIES

NAME OF SOCIETY	TOTAL NUMBER MEMBERS WHOSE DEGREES WERE FOUND	PERCENTAGES			
		Total M.D.	M.D. Only	M.D. and A.B. or Equivalent	M.D. and Ph.D.
American Surgical Association............	169	100	55	43	2
Association of American Physicians.......	147	100	32	63	5
American Orthopedic Association.........	116	100	62	37	1
American Association of Obstetricians and Gynecologists	167	100	73	24	3
American Pediatric Society...............	66	100	30	67	3
American Laryngological, Rhinological, and Otological Society	196	100	66	33	1
Totals........................	861	100	56	42	2

TABLE 2.—ANALYSIS OF SCHOLASTIC DEGREES OF MEMBERS OF SOCIE-TIES COVERING THE FUNDAMENTAL MEDICAL SCIENCES

NAME OF SOCIETY	TOTAL NUMBER MEMBERS WHOSE DEGREES WERE FOUND	PERCENTAGES					
		Total M.D.	M.D. Only	M.D. and A.B. or Equiv-alent	M.D. and Ph.D.	Ph.D.	Other De-grees
American Association of Anatomists	283	64	23	36	4	24	12
American Physiological Society....	223	54	26	18	10	37	8
American Society of Biological Chemistry	153	41	13	16	12	50	9
American Bacteriologists	335	47	24	20	3	23	30
American Association of Patholo-gists and Bacteriologists.......	316	95	40	52	3	2	3
American Society for Experimental Pathology....................	40	100	30	60	10	0	0
American Society for Pharmacology and Experimental Therapeutics .	74	87	49	26	12	13	0
American Society of Experimental Biology and Medicine.........	283	68	24	38	6	28	4
American Psychopathological Asso-ciation	44	84	39	36	9	16	0
American Association for Cancer Research	89	94	40	49	4	3	2
Total.................	1840	68	28	34	6	22	10
Compare with Analysis of Certain Clinical Med-ical Societies (Table 1).......	861	100	56	42	2	0	0
Who's Who in America (1915 edi-tion, selected names of those engaged in physical, chemical, or biologic sciences).........	3446	48	20	26	2	23	29

An analysis of the scholastic degrees of the societies covering the fundamental medical sciences is shown in Table 2.

In these, the possession of the M.D. degree is not obligatory for membership. Of the total 1840 members, 68 per cent. have the M.D. degree, 28 per cent. the M.D. only, 34 per cent. the M.D. with the bachelor's degree, 6 per cent. the M.D. and the Ph.D., 22 per cent. the Ph.D. without the M.D., and 10 per cent. neither the M.D. nor the Ph.D. The percentage of those having the M.D. without the Ph.D. (62) is nearly three times that of those having the Ph.D. without the M.D. (22). When to the number of these members is added the number of men having similar attainments who are members of the clinical medical societies, we find that 73 per cent. of the total 2701 have the M.D. degree, or the M.D. with the A.B. degree or its equivalent. Thus, it would seem that 73 per cent. of the men who have been responsible for the progress of American medicine started with only the scholastic equipment, at least so far as is indicated by their degrees, of the men now entering upon the study of specialties in medicine, while only 15 per cent. have the Ph.D. or D.Sc. degree.

Probably one-third of the 2701 members of the medical societies here studied are duplicates. In order to get a larger list and at the same time cover a broader field, I have made for comparison a similar analysis of the earned degrees of 3446 persons engaged in any of the physical, chemical, or biologic sciences (including medicine), whose names appear in the 1915 edition of *Who's Who in America*. The inclusion of a name in this publication indicates that its holder has attained a certain amount of public eminence, though not necessarily of a kind indicated by his degree. An analysis of the degrees of these 3446 persons shows that 48 per cent. have the M.D. degree, 20 per cent. have the M.D. only, 26 per cent. have the M.D. plus the A.B. or its equivalent, 2 per cent. have the M.D. plus the Ph.D., 23 per cent. have the Ph.D. without the M.D., and 29 per cent. have degrees other than M.D. or Ph.D. It therefore appears that in the field of physical, chemical, and biologic sciences the sort of eminence indicated by registry in *Who's Who* has been attained by twice as many with the degree of M.D. as with the degree of Ph.D.

An analysis of similarly selected names in *American Men of Science* was begun, but abandoned since it was found that the latest (1910) edition does not include the names of many of the younger men who are largely responsible for the present progress of American medicine.

Until the later years of the last century the teaching of medicine in America, except in a very few schools, was a travesty on pedagogy. During the present century it has probably improved more than the teaching of any other science. Today the man who obtains the M.D. degree from an institution with the equivalent of the "Minnesota standard," *i. e.*, including a final year's hospital or laboratory work, probably has quite as much scientific ability as the man who obtains the Ph.D. or D.Sc. degree from the same institution. This seems to be proved by the time he must study, by the character of the subject-matter of his studies, and by the probability of his accomplishing something in science in after-life. If this be true and the M.D., Ph.D., and D.Sc. degrees from high-grade institutions represent an equivalent training, it must then appear that the three years of graduate training in a special branch of medicine now offered by the University of Minnesota should result in scientific ability just three years "to the good" of that represented by any one of the three doctorate degrees.

DR. JOHN B. MURPHY—AN APPRECIATION*

WILLIAM J. MAYO

Dr. John B. Murphy possessed those intellectual, physical, and personal qualities which make a surgeon. After graduating from Rush Medical College in 1879 and serving an internship in Cook County Hospital, Dr. Murphy went to Vienna and came under the direction of that master surgeon, Billroth, then at the height of his great career. Billroth was a man of charming personality and most original mind, and his students today fill the chairs of surgery in many Teutonic universities. During these formative years of Dr. Murphy's European sojourn Albert was also one of his favorite teachers. Few men ever equaled Albert's ability logically to present clinical surgery. Fired with zeal, Dr. Murphy returned home and came under the influence of the father of modern surgery in the West,—Christian Fenger,—who was unequaled as a teacher of surgical pathology. Dr. Murphy combined the qualities of Billroth, Albert, and Fenger.

The reputation of a surgeon, in the final analysis, must rest upon originality, teaching by word of mouth, teaching by the printed word, surgical judgment, and operative skill.

Dr. Murphy had a marvelously fertile and original mind. Possessing a brilliant surgical imagination, he early deviated from the beaten paths and invaded new territory, and yet with such acumen that nothing which he originated has failed to live. Like those of the great musicians, his productions are still masterpieces; they mark epochs in surgical progress. He made the experimental laboratory a handmaiden to surgery, and carefully investigated every detail of his constructive work by animal experimentation before applying it to man.

As a teacher of surgery by word of mouth he had, in my opinion, no equal. Clear and logical, he started with facts about which there could be no dispute, progressed from these facts toward new ground, yet along pathways more or less familiar to all, and finally, taking us by the hand,

so to speak, he led the way to new truths by the light of his surgical genius.

As a writer he was prolific. His early work was in the field of abdominal surgery. The Murphy button taught us to solve many problems connected with gastro-intestinal surgery. His monograph on "Ileus" still stands a monument to his scientific ability. The history of surgery of the appendix, pelvis, and upper abdomen, as well as of the kidney, shows evidences of his genius. Dr. Murphy next developed surgery of the lungs, and in the oration on surgery delivered at Denver in 1898 he laid the foundation for modern surgery of the lungs; so far ahead of his time was this that we have only of late awakened to an appreciation of its value. Dr. Murphy's work on surgery of the nervous system helped to lay the foundation for the present practice, and again his latest work on bones and joints, in which he was engaged during the closing years of his life, is perhaps the greatest contribution to these subjects of our generation.

Dr. Murphy was skilful as an operator, of fine judgment, humane, sane, sound, and free from fads. What surgeon has not felt, on seeing him operate, a just pride in the science and art of surgery, and expressed the hope that in the event he or a member of his family must have an operation, so good a surgeon as Dr. Murphy might perform it?

The American surgical profession has lost its leading spirit. In Dr. Murphy's death at the age of fifty-eight well may we regret the unfilled twelve years which go to make up the allotted span of man. And yet, when we review what he has done, we freely acknowledge that even in the time the light lasted he accomplished more than any other surgeon of his time.

IN MEMORIAM

DR. EMIL HESSEL BECKMAN
1872-1916

Dr. Emil Hessel Beckman was born February 15, 1872, at Grundy Center, Iowa. He was graduated from Iowa College at Grinnell, Iowa, in 1894, with the degree of Bachelor of Philosophy. After four years of service in the public schools as a teacher of Latin and Greek and as high school principal, he entered the College of Medicine and Surgery of the University of Minnesota, from which he was graduated in 1901. During his senior year in medicine he served as intern in the City and County Hospital of St. Paul, Minnesota. In July, 1901, he became an assistant bacteriologist in the laboratory of the Minnesota State Board of Health at the State University, a position which he held for four years. Much of his time was spent in investigating epidemics of diphtheria, smallpox, scarlet fever, etc., a work for which he was especially adapted. With Wesbrook, Wilson, and McDaniel he was engaged in researches on the types and distribution of the Bacillus diphtheriæ, the means of isolating and identifying the Bacillus typhosus from various sources, and hemorrhagic septicemia in domestic animals. His taste for surgery may have developed in the large amount of experimental work on animals done during these investigations.

In July, 1905, he was appointed city physician in Minneapolis, thus being placed in charge of the city hospital. In addition to his duties as superintendent he held a gynecologic service, which gave him an opportunity to obtain some experience in surgery. After a year and nine months in this position he left it to accept work in the Mayo Clinic on April 1, 1907.

Dr. Beckman's first position in the Mayo Clinic was that of first assistant to Dr. C. H. Mayo. This post he held for four years. Early he evinced the keen clinical and surgical judgment which stood him so well in hand when later he became the head of Surgical Section 4 in the

Mayo Clinic, his position at the time of his death.   Here his work excited the admiration of all who saw it.   His fine intuition guided him clearly along the difficult path of decision as to when to withhold and when to use his rare skill for the best interest of his patient.   While his work covered the field of general surgery, his splendid technic was most evidenced in fine dissections of the cervical region in the presence of tuberculosis and cancer, in the correction of deformities of the nose and mouth, and in operations on the thorax, lungs, brain, spinal cord, and nerve ganglia.

Dr. Beckman both spoke and wrote clear, correct, and forceful English.   During the nine and one-half years he was in the Mayo Clinic he became the author of thirty scientific papers.

Dr. Beckman was a member of the Olmsted County (Minnesota) Medical Society, the Southern Minnesota Medical Association, the Minnesota State Medical Society, the Minnesota Academy of Medicine, the Colorado State Medical Society, the American Medical Association, the Interurban Surgical Association (of which he was president at the time of his death), and of the American Surgical Association. He was head of Section 4 of the Surgical Division of the Mayo Clinic, and Associate Professor of Surgery on The Mayo Foundation of the University of Minnesota.   He was president of the Olmsted County (Minnesota) Automobile Club, a director of the Rochester, Minnesota, Commercial Club, and a member of the Royal Arch Masons.

On January 1, 1902, he was married to Miss Jessie Sayre, of Odebolt, Iowa.   He was the father of two children, Catherine, aged eleven, and Ruth, aged seven.

Dr. Beckman was taken sick October 31, 1916, with an infection of Staphylococcus pyogenes aureus.   The infection began on his nasal septum, but rapidly spread to the other structures of the head, and then became general, causing his death at 10 p. m. on November 7, 1916, after eight days' illness.

His desire to do the very best possible for the good of his patients, to keep fully abreast of the literature of his profession, to be the devoted companion of his wife and children, and to fulfil in the largest measure his duties as a citizen of the community in which he lived, combined to drive him at a speed constantly approaching the limit of his physical capacity.   There is no doubt that when sickness came his resisting power was not high.   His death was due not to infection alone, but to the strenuous work of a none too strong physique.

'16—62

RESOLUTIONS

Adopted at the Joint Memorial Meeting of the Olmsted County Medical Society, the Mayo Clinic, and The Mayo Foundation, November 8, 1916.

WHEREAS, Our beloved friend, Dr. Emil Hessel Beckman, has passed from our midst, we, as members of the Olmsted County Medical Society, the Mayo Clinic, and The Mayo Foundation, of all of which he was a valued member, desire to express our sorrow.

He will ever remain in our memories as an ideal in every walk of life, be it as citizen, surgeon, or friend, and we regard his loss as irreparable. A brave man, honest and generous, with strong intellect and absolute devotion to principle, he always endeavored to elevate his profession, and constantly labored to advance its interests. Broad-minded and singularly free from narrow prejudice, his strong personality inspired trust, confidence, and love in all with whom he came in contact.

Therefore, Be it resolved that we extend our deepest sympathy to his family, and that a written expression of the same be given to them.

Be it also resolved, That these resolutions be made a matter of record in the respective societies.

Committee:
- W. F. BRAASCH,
- E. F. KILBOURNE,
- C. T. GRANGER.

INDEX OF CONTRIBUTORS

BIBLIOGRAPHIC INDEX

INDEX OF SUBJECTS

Cholesterol content of blood of goats,
        effect of mange on, 675, 676
        of pregnancy on, 686
        technical details of chemical anal-
            ysis, 688
    feeding, effect of, on cholesterol content
        of goats' blood, 671
    in gall-stones, 278
    metabolism, 671
    retention as factor in cell-proliferation,
        693
Cirrhosis of liver, splenectomy in, 615, 635
Clinicopathologic nomenclature of mam-
        mary conditions, 484
    standardization and efficiency, 476
Coffey's procedure in cancer of rectum and
        rectosigmoid, 327
Colectomy, 907
    indications for, 907
    technic, 912
Collapse, tracheal, in thyroidectomy, 549
    treatment of bronchiectasis, 763
Colon bacillus as cause of gastric and duod-
        enal ulcer, 80
    lymphatics of, 909
    right, removal of, 907
        indications, 907
        technic, 912
Colostomy, Littlewood's method, in cancer
        of rectum, 349
    Mixter's method, in cancer of rectum, 350
Common bile-duct, dilatation of, after
        cholecystectomy, 291
        rupture of, associated with subphrenic
            abscess, 302
Congenital absence of gallbladder, 268
Constipation, colectomy in, 908
Corpora oryzoidea in knee-joint, 866
Cretinism, alpha-iodin compound in, effect
        of, 522
Cripps' operation for cancer of rectum and
        rectosigmoid, 330
Crucial ligament, anterior, 854
        posterior, 854
        rupture of, 862
Cystadenoma of palate, 14, 16
Cystitis after prostatectomy, 446
Cystoscopic examination in diverticula of
        bladder, 410
Cysts, embryonal, of larynx, 27, 28
    of epiglottis, 23, 27

Cysts of larynx, 23
    etiology, 27
    pathology, 27
    theories as to origin, 28
    treatment, 28
    of spinal cord, 849
    of vocal cords, 23, 27
    retention, of larynx, 27
Cytology of blood of goats, 655–670

Dental neuritis, pulpitis, and myositis,
        elective localization of streptococcus
        from case of, 30–44
    research in preventive medicine, 960
Diagnosis, abdominal, element of error in,
        927
    surgical, x-rays in, 940
Digitalis in exophthalmic goiter, 536
Dilatation of common bile-duct after
        cholecystectomy, 291
Diverticula of bladder, 404
        acquired, 405
        clinical data, 410
        congenital, 405
        cystoscopic examination, 410
        etiology, 405
        location of opening, 411
        operative mortality, 414
        postmortem findings, 415
        previous diseases, 410
        routes for radical operation, 409
        treatment, medical, 413
            surgical, 414
                complications of, 414
        urinalysis in, 412
        urinary symptoms, 410
        x-rays in diagnosis, 411
Doloro genetic zones of trifacial neuralgia,
        734
Drainage in bronchiectasis, 765
    in empyema of gallbladder, 273
    in one-stage lobectomy in bronchiectasis,
        783
    of gallbladder, 272
Ductless glands, 491
        and hibernation, relation, 493
Duodenal contents, blood-derived pigments
        in, after splenectomy for pernicious
        anemia, 721
    spasm from roentgenologic point of view,
        102, 114